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(54) Title: INHIBITORS OF INTERLEUKIN-1 $\beta$  CONVERTING ENZYME

## (57) Abstract

The present invention relates to novel classes of compounds which are inhibitors of interleukin-1 $\beta$  converting enzyme. The ICE inhibitors of this invention are characterized by specific structural and physicochemical features. This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting ICE activity and consequently, may be advantageously used as agents against IL-1-, apoptosis-, IGIF-, and IFN- $\gamma$ -mediated diseases, inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases, degenerative diseases, and necrotic diseases. This invention also relates to methods for inhibiting ICE activity, for treating interleukin-1-, apoptosis-, IGIF- and IFN- $\gamma$ -mediated diseases and decreasing IGIF and IFN- $\gamma$  production using the compounds and compositions of this invention. This invention also relates to methods for preparing N-acetylamino compounds.

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INHIBITORS OF INTERLEUKIN-1 $\beta$  CONVERTING ENZYMETECHNICAL FIELD OF THE INVENTION

The present invention relates to novel  
5 classes of compounds which are inhibitors of  
interleukin-1 $\beta$  converting enzyme ("ICE"). This  
invention also relates to pharmaceutical compositions  
comprising these compounds. The compounds and  
pharmaceutical compositions of this invention are  
10 particularly well suited for inhibiting ICE activity  
and consequently, may be advantageously used as agents  
against interleukin-1- ("IL-1"), apoptosis-, interferon  
gamma inducing factor- ("IGIF") and interferon- $\gamma$ -  
("IFN- $\gamma$ ") mediated diseases, including inflammatory  
15 diseases, autoimmune diseases, destructive bone,  
proliferative disorders, infectious diseases and  
degenerative diseases. This invention also relates to  
methods for inhibiting ICE activity, and decreasing  
IGIF production and IFN- $\gamma$  production and methods for  
20 treating interleukin-1-, apoptosis-, IGIF- and IFN- $\gamma$ -  
mediated diseases using the compounds and compositions  
of this invention. This invention also relates to  
methods of preparing N-acylamino compounds.

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BACKGROUND OF THE INVENTION

Interleukin 1 ("IL-1") is a major pro-inflammatory and immunoregulatory protein that stimulates fibroblast differentiation and proliferation, the production of prostaglandins, collagenase and phospholipase by synovial cells and chondrocytes, basophil and eosinophil degranulation and neutrophil activation. Oppenheim, J.H. et al, Immunology Today, 7, pp. 45-56 (1986). As such, it is involved in the pathogenesis of chronic and acute inflammatory and autoimmune diseases. For example, in rheumatoid arthritis, IL-1 is both a mediator of inflammatory symptoms and of the destruction of the cartilage proteoglycan in afflicted joints. Wood, D.D. et al., Arthritis Rheum. 26, 975, (1983); Pettipher, E.J. et al., Proc. Natl. Acad. Sci. UNITED STATES OF AMERICA 71, 295 (1986); Arend, W.P. and Dayer, J.M., Arthritis Rheum. 38, 151 (1995). IL-1 is also a highly potent bone resorption agent. Jandiski, J.J., J. Oral Path 17, 145 (1988); Dewhirst, F.E. et al., J. Immunol. 8, 2562 (1985). It is alternately referred to as "osteoclast activating factor" in destructive bone diseases such as osteoarthritis and multiple myeloma. Bataille, R. et al., Int. J. Clin. Lab. Res. 21(4), 283 (1992). In certain proliferative disorders, such as acute myelogenous leukemia and multiple myeloma, IL-1 can promote tumor cell growth and adhesion. Bani, M.R., J. Natl. Cancer Inst. 83, 123 (1991); Vidal-Vanaclocha, F., Cancer Res. 54, 2667 (1994). In these disorders, IL-1 also stimulates production of other cytokines such as IL-6, which can modulate tumor development (Tartour et al., Cancer Res. 54, 6243 (1994). IL-1 is predominantly produced by peripheral blood monocytes as part of the inflammatory response



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and exists in two distinct agonist forms, IL-1 $\alpha$  and IL-1 $\beta$ . Mosely, B.S. et al., Proc. Nat. Acad. Sci., 84, pp. 4572-4576 (1987); Lonnemann, G. et al., Eur. J. Immunol., 19, pp. 1531-1536 (1989).

5 IL-1 $\beta$  is synthesized as a biologically inactive precursor, pIL-1 $\beta$ . pIL-1 $\beta$  lacks a conventional leader sequence and is not processed by a signal peptidase. March, C.J., Nature, 315, pp. 641-647 (1985). Instead, pIL-1 $\beta$  is cleaved by  
10 interleukin-1 $\beta$  converting enzyme ("ICE") between Asp-116 and Ala-117 to produce the biologically active C-terminal fragment found in human serum and synovial fluid. Sleath, P.R., et al., J. Biol. Chem., 265, pp. 14526-14528 (1992); A.D. Howard et al., J. Immunol., 147, pp. 2964-2969 (1991). ICE is a cysteine protease localized primarily in monocytes. It converts  
15 precursor IL-1 $\beta$  to the mature form. Black, R.A. et al., FEBS Lett., 247, pp. 386-390 (1989); Kostura, M.J. et al., Proc. Natl. Acad. Sci. UNITED STATES OF AMERICA, 86, pp. 5227-5231 (1989). Processing by ICE  
20 is also necessary for the transport of mature IL-1 $\beta$  through the cell membrane.

ICE, or its homologs, also appears to be involved in the regulation of programmed cell death or  
25 apoptosis. Yuan, J. et al., Cell, 75, pp. 641-652 (1993); Miura, M. et al., Cell, 75, pp. 653-660 (1993); Nett-Fiordalisi, M.A. et al., J. Cell Biochem., 17B, p. 117 (1993). In particular, ICE or ICE homologs are thought to be associated with the regulation of  
30 apoptosis in neurodegenerative diseases, such as Alzheimer's and Parkinson's disease. Marx, J. and M. Baringa, Science, 259, pp. 760-762 (1993); Gagliardini, V. et al., Science, 263, pp. 826-828 (1994).  
Therapeutic applications for inhibition of apoptosis

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may include treatment of Alzheimer's disease, Parkinson's disease, stroke, myocardial infarction, spinal atrophy, and aging.

ICE has been demonstrated to mediate apoptosis (programmed cell death) in certain tissue types. Steller, H., Science, 267, p. 1445 (1995); Whyte, M. and Evan, G., Nature, 376, p. 17 (1995); Martin, S.J. and Green, D.R., Cell, 82, p. 349 (1995); Alnemri, E.S., et al., J. Biol. Chem., 270, p. 4312 (1995); Yuan, J. Curr. Opin. Cell Biol., 7, p. 211 (1995). A transgenic mouse with a disruption of the ICE gene is deficient in Fas-mediated apoptosis (Kuida, K. et al., Science 267, 2000 (1995)). This activity of ICE is distinct from its role as the processing enzyme for pro-IL1 $\beta$ . It is conceivable that in certain tissue types, inhibition of ICE may not affect secretion of mature IL-1 $\beta$ , but may inhibit apoptosis.

Enzymatically active ICE has been previously described as a heterodimer composed of two subunits, p20 and p10 (20kDa and 10kDa molecular weight, respectively). These subunits are derived from a 45kDa proenzyme (p45) by way of a p30 form, through an activation mechanism that is autocatalytic. Thornberry, N.A. et al., Nature, 356, pp. 768-774 (1992). The ICE proenzyme has been divided into several functional domains: a prodomain (p14), a p22/20 subunit, a polypeptide linker and a p10 subunit. Thornberry et al., supra; Casano et al., Genomics, 20, pp. 474-481 (1994).

Full length p45 has been characterized by its cDNA and amino acid sequences. PCT patent applications WO 91/15577 and WO 94/00154. The p20 and p10 cDNA and amino acid sequences are also known. Thornberry et al., supra. Murine and rat ICE have also been sequenced and cloned. They have high amino acid and

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nucleic acid sequence homology to human ICE. Miller, D.K. et al., Ann. N.Y. Acad. Sci., 696, pp. 133-148 (1993); Molineaux, S.M. et al., Proc. Nat. Acad. Sci., 90, pp. 1809-1813 (1993). The three-dimensional structure of ICE has been determined at atomic resolution by X-ray crystallography. Wilson, K.P., et al., Nature, 370, pp. 270-275 (1994). The active enzyme exists as a tetramer of two p20 and two p10 subunits.

10        Additionally, there exist human homologs of ICE with sequence similarities in the active site regions of the enzymes. Such homologs include TX (or ICE<sub>rel-II</sub> or ICH-2) (Faucheu, et al., EMBO J., 14, p. 1914 (1995); Kamens J., et al., J. Biol. Chem., 270, p. 15250 (1995); Nicholson et al., J. Biol. Chem., 270 15870 (1995)), TY (or ICE<sub>rel-III</sub>) (Nicholson et al., J. Biol. Chem., 270, p. 15870 (1995); ICH-1 (or Nedd-2) (Wang, L. et al., Cell, 78, p. 739 (1994)), MCH-2, (Fernandes-Alnemri, T. et al., Cancer Res., 55, p. 2737 (1995), CPP32 (or YAMA or apopain) (Fernandes-Alnemri, T. et al., J. Biol. Chem., 269, p. 30761 (1994); Nicholson, D.W. et al., Nature, 376, p. 37 (1995)), and CMH-1 (or MCH-3) (Lippke, et al., J. Biol. Chem., (1996); Fernandes-Alnemri, T. et al., Cancer Res., (1995)). Each of these ICE homologs, as well as ICE itself, is capable of inducing apoptosis when overexpressed in transfected cell lines. Inhibition of one or more of these homologs with the peptidyl ICE inhibitor Tyr-Val-Ala-Asp-chloromethylketone results in inhibition of apoptosis in primary cells or cell lines. Lazebnik et al., Nature, 371, p. 346 (1994). The compounds described herein are also capable of inhibiting one or more homologs of ICE (see Example 5). Therefore, these compounds may be used to inhibit apoptosis in tissue types that contain ICE homologs, but which do not contain active ICE or produce mature

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IL-1 $\beta$ .

Interferon-gamma inducing factor (IGIF) is an approximately 18-kDa polypeptide that stimulates T-cell production of interferon-gamma (IFN- $\gamma$ ). IGIF is produced by activated Kupffer cells and macrophages in vivo and is exported out of such cells upon endotoxin stimulation. Thus, a compound that decreases IGIF production would be useful as an inhibitor of such T-cell stimulation which in turn would reduce the levels of IFN- $\gamma$  production by those cells.

IFN- $\gamma$  is a cytokine with immunomodulatory effects on a variety of immune cells. In particular, IFN- $\gamma$  is involved in macrophage activation and Th1 cell selection (F. Belardelli, APMIS, 103, p. 161 (1995)). IFN- $\gamma$  exerts its effects in part by modulating the expression of genes through the STAT and IRF pathways (C. Schindler and J.E. Darnell, Ann. Rev. Biochem., 64, p. 621 (1995); T. Taniguchi, J. Cancer Res. Clin. Oncol., 121, p. 516 (1995)).

Mice lacking IFN- $\gamma$  or its receptor have multiple defects in immune cell function and are resistant to endotoxic shock (S. Huang et al., Science, 259, p. 1742 (1993); D. Dalton et al., Science, 259, p. 1739 (1993); B. D. Car et al., J. Exp. Med., 179, p. 1437 (1994)). Along with IL-12, IGIF appears to be a potent inducer of IFN- $\gamma$  production by T cells (H. Okamura et al., Infection and Immunity, 63, p. 3966 (1995); H. Okamura et al., Nature, 378, p. 88 (1995); S. Ushio et al., J. Immunol., 156, p. 4274 (1996)).

IFN- $\gamma$  has been shown to contribute to the pathology associated with a variety of inflammatory, infectious and autoimmune disorders and diseases. Thus, compounds capable of decreasing IFN- $\gamma$  production

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would be useful to ameliorate the effects of IFN- $\gamma$  related pathologies.

The biological regulation of IGIF and thus IFN- $\gamma$  has not been elucidated. It is known that IGIF is synthesized as a precursor protein, called "pro-IGIF". It has been unclear, however, how pro-IGIF is cleaved and whether its processing has biological importance.

Accordingly, compositions and methods capable of regulating the conversion of pro-IGIF to IGIF would be useful for decreasing IGIF and IFN- $\gamma$  production in vivo, and thus for ameliorating the detrimental effects of these proteins which contribute to human disorders and diseases.

However, ICE and other members of the ICE/CED-3 family have not previously been linked to the conversion of pro-IGIF to IGIF or to IFN- $\gamma$  production in vivo.

ICE inhibitors represent a class of compounds useful for the control of inflammation or apoptosis or both. Peptide and peptidyl inhibitors of ICE have been described. PCT patent applications WO 91/15577; WO 93/05071; WO 93/09135; WO 93/14777 and WO 93/16710; and European patent application 0 547 699. Such peptidyl inhibitors of ICE has been observed to block the production of mature IL-1 $\beta$  in a mouse model of inflammation (vide infra) and to suppress growth of leukemia cells *in vitro* (Estrov et al., Blood 84, 380a (1994)). However, due to their peptidic nature, such inhibitors are typically characterized by undesirable pharmacologic properties, such as poor cellular penetration and cellular activity, poor oral absorption, poor stability and rapid metabolism. Plattner, J.J. and D.W. Norbeck, in Drug Discovery

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Technologies, C.R. Clark and W.H. Moos, Eds. (Ellis Horwood, Chichester, England, 1990), pp. 92-126. This has hampered their development into effective drugs.

Non-peptidyl compounds have also been reported to inhibit ICE in vitro. PCT patent application WO 95/26958; US Patents 5,552,400; Dolle et al., J. Med. Chem., 39, pp. 2438-2440 (1996); However, it is not clear whether these compounds have the appropriate pharmacological profile to be therapeutically useful.

Additionally, current methods for the preparation of such compounds are not advantageous. These methods use tributyltin hydride, a toxic, moisture sensitive reagent. Thus, these methods are inconvenient to carry out, pose a health risk and create toxic-waste disposal problems. Furthermore, it is difficult to purify compounds prepared by these methods.

Accordingly, the need exists for compounds that can effectively inhibit the action of ICE *in vivo*, for use as agents for preventing and treating chronic and acute forms of IL-1-mediated diseases, apoptosis-, IGIF-, or IFN- $\gamma$ -mediated diseases, as well as inflammatory, autoimmune, destructive bone, proliferative, infectious, or degenerative diseases. The need also exists for methods of preparing such compounds.

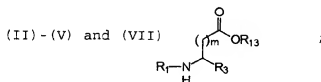
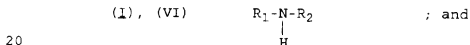
#### SUMMARY OF THE INVENTION

The present invention provides novel classes of compounds, and pharmaceutically acceptable derivatives thereof, that are useful as inhibitors of ICE. These compounds can be used alone or in combination with other therapeutic or prophylactic agents, such as antibiotics, immunomodulators or other anti-inflammatory agents, for the treatment or

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prophylaxis of diseases mediated by IL-1, apoptosis, IGIF or IFN- $\gamma$ . According to a preferred embodiment, the compounds of this invention are capable of binding to the active site of ICE and inhibiting the activity of that enzyme. Additionally, they have improved cellular potency, improved pharmacokinetics, and/or improved oral bioavailability compared to peptidyl ICE inhibitors.

It is a principal object of this invention to provide novel classes of compounds which are inhibitors of ICE represented by formulas:



wherein the various substituents are described herein.

It is a further object of this invention to provide a process of preparing N-acylamino compounds by coupling a carboxylic acid with an alloc-protected amine.

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BRIEF DESCRIPTION OF THE DRAWINGS

**Fig. 1A** ICE cleaves pro-IGIF in vivo. Cell lysates from Cos cells transfected with the various indicated expression plasmids or controls were analyzed for the presence of IGIF by separating proteins by SDS-PAGE and immunoblotting with anti-IGIF antisera (lane 1, mock transfected cells; lane 2, pro-IGIF alone; lanes 3-12, pro-IGIF in combination with ICE, ICE-C285S, CPP32, CPP32-C163S, CMH-1, CMH-1-C186S, Tx, Tx-C258S, respectively). Mobilities of pro-IGIF and the 18-kDa mature IGIF are indicated on the right. Molecular weight markers in kDa are shown on the left (Example 23).

**Fig. 1B** ICE cleaves pro-IGIF at the authentic processing site in vitro as shown by Coomassie blue staining of proteolytic reaction products separated by SDS-PAGE (Example 23). The proteases and inhibitors used were: lane 1, buffer control; lane 2, 0.1 nM ICE; lane 3, 1 nM ICE; lanes 4 and 5, 1 nM ICE with 10 nM Cbz-Val-Ala-Asp-[(2,6-dichlorobenzoyl)oxymethyl] ketone and 100 nM Ac-Tyr-Val-Ala-Asp-aldehyde, respectively; lanes 6 and 7, 15 nM CPP32 with and without 400 nM Ac-Asp-Glu-Val-Asp-aldehyde (D. W. Nicholson et al., Nature, 376, p. 37 (1995)), respectively; lane 8, 100 nM CMH-1; lane 9, 10 units/ml granzyme B; and M, molecular weight markers in kDa.

**Fig. 1C** ICE cleavage converts inactive pro-IGIF to active IGIF which induces IFN- $\gamma$  production in Th1 helper cells. Uncleaved (Pro-IGIF), ICE-cleaved (Pro-IGIF/ICE), CPP32-cleaved (Pro-IGIF/CPP32), and recombinant mature IGIF (rIGIF) were incubated with



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A.E7 Th1 cells at 12 ng/ml (open bar) and 120 ng/ml (hatched bar) for eighteen hours and the levels of IFN- $\gamma$  released into the culture medium assayed by ELISA (Example 23). A.E7 cells cultured with buffer, ICE  
5 alone (ICE) or CPP32 alone (CPP32) were assayed similarly for negative controls. The numbers represent the average of three determinations.

**Fig. 2A** Mature IGIF (18-kDa) is produced by Cos cells co-transfected with pro-IGIF and ICE-expressing  
10 plasmids. Cell lysates (left) and conditioned medium (right) from Cos cells transfected with a pro-IGIF expression plasmid in the absence (-) or presence of an expression plasmid encoding wild type (ICE) or inactive mutant (ICE-C285S) ICE. Transfected cells were  
15 metabolically labeled with  $^{35}\text{S}$ -methionine, proteins from cell lysates and conditioned medium immunoprecipitated with anti-IGIF antisera and separated by SDS-PAGE (Example 24). Mobilities of pro-IGIF and the 18-kDa mature IGIF are indicated on the right. Molecular  
20 weight markers in kDa are shown on the left.

**Fig. 2B** IFN- $\gamma$  inducing activity is detected in Cos cells co-transfected with pro-IGIF and ICE-expressing  
plasmids. Cell lysates (hatched bar) and conditioned medium (open bar) from Cos cells transfected with a  
25 pro-IGIF expression plasmid in the absence (Pro-IGIF) or presence (Pro-IGIF/ICE) of an expression plasmid encoding wild type (ICE) were assayed for IFN- $\gamma$  levels (ng/ml) by ELISA. Cos cells transfected with buffer (Mock) or an ICE-expressing plasmid alone (ICE) served  
30 as negative controls (Example 24).

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Fig. 3A Kupffer cells from mice lacking ICE are defective in the export of IGIF. Kupffer cells from wild type mice (ICE +/+) or ICE-deficient mice homozygous for an ICE mutation (ICE -/-) were isolated and primed with LPS for three hours. The levels of immunoreactive IGIF polypeptides in the conditioned media (ng/ml) of wild type cells were measured by ELISA (Example 25). N.D. (not detectable) indicates that the IGIF concentration was less than 0.1 ng/ml.

Fig. 3B Kupffer cells from mice lacking ICE are defective in the export of mature IGIF. Kupffer cells from wild type mice (ICE +/+) or ICE deficient mice homozygous for an ICE mutation (ICE -/-) were isolated and primed with LPS for three hours. Primed cells were metabolically labeled with <sup>35</sup>S-methionine, proteins from cell lysates and conditioned medium immunoprecipitated with anti-IGIF antisera and separated by SDS-PAGE (Example 25). Mobilities of pro-IGIF and the 18-kDa mature IGIF are indicated on the right. Molecular mass markers in kDa are shown on the left.

Fig. 3C Serum from ICE-deficient mice contains reduced levels of IGIF. Serum samples from wild type mice (ICE +/+) or ICE deficient mice homozygous for an ICE mutation (ICE -/-) were assayed for IGIF levels (ng/ml) by ELISA (Example 25).

Fig. 3D Serum from ICE-deficient mice contains reduced levels of IFN- $\gamma$ . Serum samples from wild type mice (ICE +/+) or ICE deficient mice homozygous for an ICE mutation (ICE -/-) were assayed for IFN- $\gamma$  levels (ng/ml) by ELISA (Example 25).

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**Fig. 4** Serum IFN- $\gamma$  levels are significantly reduced in ICE-deficient mice after an acute challenge with LPS (Example 26). Serum samples from wild type mice (filled squares) or ICE-deficient mice (filled circles) were assayed for IFN- $\gamma$  levels (ng/ml) by ELISA as a function of time (hours) after LPS challenge. Temperatures of the animals during the time course in degrees Celcius is shown for wild type mice (open squares) or ICE-deficient mice (open circles).

**Fig. 5** The ICE inhibitor, AcYVAD-aldehyde (AcYVAD-CHO), inhibits LPS-stimulated IL-1 $\beta$  and IFN- $\gamma$  synthesis by human peripheral blood mononuclear cells (PBMC). Percent (%) inhibition as a function of inhibitor concentration ( $\mu$ M) is shown for IL-1 $\beta$  (open squares) and IFN- $\gamma$  (open diamonds) synthesis.

**Fig. 6** Compound **214e** inhibits IL-1 $\beta$  production in LPS-challenged mice. Serum samples from CD1 mice were assayed for IL-1 $\beta$  levels (pg/ml) by ELISA after LPS challenge. Compound **214e** was administered by intraperitoneal (IP) injection one hour after LPS challenge. Blood was collected seven hours after LPS challenge (see Example 7).

**Fig. 7** Compound **217e** inhibits IL-1 $\beta$  production in LPS-challenged mice. Serum samples from CD1 mice were assayed for IL-1 $\beta$  levels (pg/ml) by ELISA after LPS challenge. Compound **217e** was administered by intraperitoneal (IP) injection one hour after LPS challenge. Blood was collected seven hours after LPS challenge (see Example 7).

**Fig. 8** Compound **214e**, but not compound **217e**,

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inhibits IL-1 $\beta$  production in LPS-challenged mice when administered by oral gavage. This assay measures oral absorption under similar conditions as those described for Figs. 6 and 7. These results indicates that **214e** is potentially orally active as an ICE inhibitor (see Example 7).

**Fig. 9** Compound **214e** and analogs of **214e** also inhibit IL-1 $\beta$  production after IP administration. These results were obtained in the assay described for **Figs. 6 and 7** and Example 7.

**Fig. 10** Compound **214e**, and analogs of **214e**, also inhibit IL-1 $\beta$  production after oral (PO) administration. These results were obtained in the assay described for **Figs. 6 and 7** and Example 7.

**Figs. 11A/B** Compounds **302** and **304a** show detectable blood levels when administered orally (50mg/kg, in 0.5 % carboxymethylcellulose) to mice. Blood samples were collected at 1 and 7 hours after dosing. Compounds **302** and **304a** are prodrugs of **214e** and are metabolized to **214e in vivo**. Compound **214e** shows no blood levels above 0.10  $\mu$ g/ml when administered orally (Example 8).

**Fig. 12** Compound **412f** blocks the progression of type II collagen-induced arthritis in male DBA/1J mice (Wooley, P.H., Methods in Enzymology, 162, pp. 361-373 (1988) and Geiger, T., Clinical and Experimental Rheumatology, 11, pp. 515-522 (1993)). Compound **412f** was administered twice a day (10, 25 and 50mg/kg), approximately 7h apart, by oral gavage. Inflammation was measured on the Arthritis Severity Score on a 1 to 4 scale of increasing severity. The scores of the two front paws were added to give the final score (see Example 21).

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**Fig. 13** Compound **412d** blocks the progression of type II collagen-induced arthritis in male DBA/1J mice. The results were obtained as described for **Fig. 12** and in Example 21.

- 5 **Fig. 14** Compound **696a** blocks the progression of type II collagen-induced arthritis in male DBA/1J mice. The results were obtained as described for **Fig. 12** and in Example 21.

#### ABBREVIATIONS AND DEFINITIONS

|    | <u>Designation</u> | <u>Abbreviations</u>       |
|----|--------------------|----------------------------|
| 10 |                    | <u>Reagent or Fragment</u> |
|    | Ala                | alanine                    |
|    | Arg                | arginine                   |
|    | Asn                | asparagine                 |
| 15 | Asp                | aspartic acid              |
|    | Cys                | cysteine                   |
|    | Gln                | glutamine                  |
|    | Glu                | glutamic acid              |
|    | Gly                | glycine                    |
| 20 | His                | histidine                  |
|    | Ile                | isoleucine                 |
|    | Leu                | leucine                    |
|    | Lys                | lysine                     |
|    | Met                | methionine                 |
| 25 | Phe                | phenylalanine              |
|    | Pro                | proline                    |
|    | Ser                | serine                     |
|    | Thr                | threonine                  |
|    | Trp                | tryptophan                 |
| 30 | Tyr                | tyrosine                   |
|    | Val                | valine                     |
|    | Ac <sub>2</sub> O  | acetic anhydride           |
|    | n-Bu               | normal-butyl               |

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|    |                   |   |
|----|-------------------|---|
|    | DMF               | dimethylformamide   |
|    | DIEA              | <i>N,N</i> -diisopropylethylamine                           |
|    | EDC               | 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride |
| 5  | Et <sub>2</sub> O | diethyl ether   |
|    | EtOAc             | ethyl acetate   |
|    | Fmoc              | 9-fluorenylmethoxycarbonyl                                  |
|    | HBTU              | O-benzotriazol-1-yl- <i>N,N,N',N'</i> -tetramethyluronium   |
| 10 |                   | hexafluorophosphate   |
|    | HOBT              | 1-hydroxybenzotriazole hydrate                              |
|    | MeOH              | methanol  |
|    | TFA               | trifluoroacetic acid  |
|    | Alloc             | allyloxycarbonyl  |

15

### Definitions

The following terms are employed herein:

The term "interferon gamma inducing factor" or "IGIF" refers to a factor which is capable of stimulating the endogenous production of IFN- $\gamma$ .

The term "ICE inhibitor" refers to a compound which is capable of inhibiting the ICE enzyme. ICE inhibition may be determined using the methods described and incorporated by reference herein. The skilled practitioner realizes that an in vivo ICE inhibitor is not necessarily an in vitro ICE inhibitor. For example, a prodrug form of a compound typically demonstrates little or no activity in in vitro assays. Such prodrug forms may be altered by metabolic or other biochemical processes in the patient to provide an in vivo ICE inhibitor.

30

The term "cytokine" refers to a molecule which mediates interactions between cells.

The term "condition" refers to any disease,

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disorder or effect that produces deleterious biological consequences in a subject.

The term "subject" refers to an animal, or to one or more cells derived from an animal. Preferably, the animal is a mammal, most preferably a human. Cells may be in any form, including but not limited to cells retained in tissue, cell clusters, immortalized cells, transfected or transformed cells, and cells derived from an animal that have been physically or phenotypically altered.

The term "active site" refers to any or all of the following sites in ICE: the substrate binding site, the site where an inhibitor binds and the site where the cleavage of substrate occurs.

The term "heterocycle" or "heterocyclic" refers to a stable mono- or polycyclic compound which may optionally contain one or two double bonds or may optionally contain one or more aromatic rings. Each heterocycle consists of carbon atoms and from one to four heteroatoms independently selected from a group including nitrogen, oxygen, and sulfur. As used herein, the terms "nitrogen heteroatoms" and "sulphur heteroatoms" include any oxidized form of nitrogen or sulfur and the quaternized form of any basic nitrogen. Heterocycles defined above include, for example, pyrimidinyl, tetrahydroquinolyl, tetrahydroisoquinolinyl, purinyl, pyrimidyl, indolinyl, benzimidazolyl, imidazolyl, imidazolinoyl, imidazolidinyl, quinolyl, isoquinolyl, indolyl, pyridyl, pyrrolyl, pyrrolinyl, pyrazolyl, pyrazinyl, quinoxolyl, piperidinyl, morpholinyl, thiamorpholinyl, furyl, thienyl, triazolyl, thiazolyl,  $\beta$ -carbolinyl, tetrazolyl, thiazolidinyl, benzofuranoyl, thiamorpholinyl sulfone, benzoxazolyl, oxopiperidinyl, oxopyrroldinyl, oxoazepinyl, azepinyl, isoxazolyl,

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tetrahydropyranyl, tetrahydrofuranyl, thiadiazolyl, benzodioxolyl, benzothienyl, tetrahydrothiophenyl and sulfolanyl. Further heterocycles are described in A.R. Katritzky and C.W. Rees, eds., Comprehensive Heterocyclic Chemistry: The Structure, Reactions, Synthesis and Use of Heterocyclic Compounds, Vol. 1-8, Pergamon Press, NY (1984).

5       The term "cycloalkyl" refers to a mono- or polycyclic group which contains 3 to 15 carbons and may optionally contain one or two double bonds. Examples include cyclohexyl, adamantyl and norbornyl.

10       The term "aryl" refers to a mono- or polycyclic group which contains 6, 10, 12, or 14 carbons in which at least one ring is aromatic. Examples include phenyl, naphthyl, and tetrahydronaphthalene.

15       The term "heteroaromatic" refers to a mono- or polycyclic group which contains 1 to 15 carbon atoms and from 1 to 4 heteroatoms, each of which is selected independently from a group including sulphur, nitrogen and oxygen, and which additionally contains from 1 to 3 five or six membered rings, at least one of which is aromatic.

20       The term "alpha-amino acid" ( $\alpha$ -amino acid) refers to both the naturally occurring amino acids and other "non-protein"  $\alpha$ -amino acids commonly utilized by those in the peptide chemistry arts when preparing synthetic analogues of naturally occurring peptides, including D and L forms. The naturally occurring amino acids are glycine, alanine, valine, leucine, iso-leucine, serine, methionine, threonine, phenylalanine, tyrosine, tryptophan, cysteine, proline, histidine, aspartic acid, asparagine, glutamic acid, glutamine,  $\gamma$ -carboxyglutamic acid, arginine, ornithine and lysine.

35       Examples of "non-protein" alpha-amino acids include



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hydroxylysine, homoserine, homotyrosine, homo-phenylalanine, citrulline, kynurenine, 4-amino-phenylalanine, 3-(2-naphthyl)-alanine, 3-(1-naphthyl)-alanine, methionine sulfone, t-butyl-alanine, 5 t-butylglycine, 4-hydroxyphenylglycine, aminoalanine, phenylglycine, vinylalanine, propargyl-glycine, 1,2,4-triazolo-3-alanine, 4,4,4-trifluoro-threonine, thyrone, 6-hydroxytryptophan, 5-hydro-xytryptophan, 3-hydroxykynurenine, 3-aminotyrosine, trifluoromethyl-10 alanine, 2-thienylalanine, (2-(4-pyridyl)ethyl)-cysteine, 3,4-dimethoxy-phenylalanine, 3-(2-thiazolyl)-alanine, ibotenic acid, 1-amino-1-cyclopentane-carboxylic acid, 1-amino-1-cyclohexanecarboxylic acid, quisqualic acid, 3-trifluoromethylphenylalanine, 15 4-trifluoro-methylphenylalanine, cyclohexylalanine, cyclo-hexylglycine, thiohistidine, 3-methoxytyrosine, elastatinal, norleucine, norvaline, allosileucine, homoarginine, thioproline, dehydroproline, hydroxy-proline, isonipectotic acid, homoproline, cyclohexyl-20 glycine,  $\alpha$ -amino-n-butyric acid, cyclohexylalanine, aminophenylbutyric acid, phenylalanines substituted at the ortho, meta, or para position of the phenyl moiety with one or two of the following: a (C<sub>1</sub>-C<sub>4</sub>) alkyl, a (C<sub>1</sub>-C<sub>4</sub>) alkoxy, halogen or nitro groups or substituted 25 with a methylenedioxy group;  $\beta$ -2- and 3-thienyl-alanine,  $\beta$ -2- and 3-furanylalanine,  $\beta$ -2-, 3- and 4-pyridylalanine,  $\beta$ -(benzothienyl-2- and 3-yl)alanine,  $\beta$ -(1- and 2-naphthyl)alanine, O-alkylated derivatives of serine, threonine or tyrosine, S-alkylated cysteine, 30 S-alkylated homocysteine, O-sulfate, O-phosphate and O-carboxylate esters of tyrosine, 3-sulfo-tyrosine, 3-carboxy-tyrosine, 3-phospho-tyrosine, 4-methane sulfonic acid ester of tyrosine, 4-methane phosphonic acid ester of tyrosine, 3,5-diiodotyrosine, 3-nitro-35 tyrosine,  $\epsilon$ -alkyl lysine, and delta-alkyl ornithine.

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Any of these  $\alpha$ -amino acids may be substituted with a methyl group at the alpha position, a halogen at any aromatic residue on the  $\alpha$ -amino side chain, or an appropriate protective group at the O, N, or S atoms of the side chain residues. Appropriate protective groups are disclosed in "Protective Groups In Organic Synthesis," T.W. Greene and P.G.M. Wuts, J. Wiley & Sons, NY, NY, 1991.

The term "substitute" refers to the replacement of a hydrogen atom in a compound with a substituent group. In the present invention, those hydrogen atoms which form a part of a hydrogen bonding moiety which is capable of forming a hydrogen bond with the carbonyl oxygen of Arg-341 of ICE or the carbonyl oxygen of Ser-339 of ICE are excluded from substitution. These excluded hydrogen atoms include those which comprise an -NH- group which is alpha to a -CO- group and are depicted as -NH- rather than an X group or some other designation in the following diagrams: (a) through (t), (v) through (z).

The term "straight chain" refers to a contiguous unbranching string of covalently bound atoms. The straight chain may be substituted, but these substituents are not a part of the straight chain.

The term " $K_i$ " refers to a numerical measure of the effectiveness of a compound in inhibiting the activity of a target enzyme such as ICE. Lower values of  $K_i$  reflect higher effectiveness. The  $K_i$  value is a derived by fitting experimentally determined rate data to standard enzyme kinetic equations (see I. H. Segel, Enzyme Kinetics, Wiley-Interscience, 1975).

The term "patient" as used in this application refers to any mammal, especially humans.

The term "pharmaceutically effective amount" refers to an amount effective in treating or

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ameliorating an IL-1-, apoptosis-, IGIF- or IFN- $\gamma$ -mediated disease in a patient. The term "prophylactically effective amount" refers to an amount effective in preventing or substantially lessening

5 IL-1-, apoptosis-, IGIF or IFN- $\gamma$  mediated diseases in a patient.

The term "pharmaceutically acceptable carrier or adjuvant" refers to a non-toxic carrier or adjuvant that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof.

The term "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, ester, or salt of such ester, of a compound of this invention or any other compound which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound of this invention or an anti-ICE active metabolite or residue thereof.

Pharmaceutically acceptable salts of the compounds of this invention include, for example, those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts. Salts derived from appropriate bases include alkali metal (e.g., sodium), alkaline earth metal (e.g., magnesium), ammonium and N-(C<sub>1-4</sub> alkyl)<sub>4</sub><sup>+</sup>

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salts.

This invention also envisions the "quaternization" of any basic nitrogen-containing groups of the compounds disclosed herein. The basic nitrogen can be quaternized with any agents known to those of ordinary skill in the art including, for example, lower alkyl halides, such as methyl, ethyl, propyl and butyl chloride, bromides and iodides; dialkyl sulfates including dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; and aralkyl halides including benzyl and phenethyl bromides. Water or oil-soluble or dispersible products may be obtained by such quaternization.

The ICE inhibitors of this invention may contain one or more "asymmetric" carbon atoms and thus may occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be of the R or S configuration. Although specific compounds and scaffolds exemplified in this application may be depicted in a particular stereochemical configuration, compounds and scaffolds having either the opposite stereochemistry at any given chiral center or mixtures thereof are also envisioned.

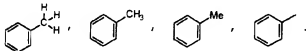
The ICE inhibitors of this invention may comprise ring structures which may optionally be substituted at carbon, nitrogen or other atoms by various substituents. Such ring structures may be singly or multiply substituted. Preferably, the ring structures contain between 0 and 3 substituents. When multiply substituted, each substituent may be picked independently of any other substituent as long as the

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combination of substituents results in the formation of a stable compound.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and administration to a mammal by methods known in the art. Typically, such compounds are stable at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

Substituents may be represented in various forms. These various forms are known to the skilled practitioner and may be used interchangeably. For 15 example, a methyl substituent on a phenyl ring may be represented in any of the following forms:



Various forms of substituents such as methyl are used herein interchangeably.

20 DETAILED DESCRIPTION OF THE INVENTION

In order that the invention herein described may be more fully understood, the following detailed description is set forth.

The ICE inhibitors of one embodiment (A) of  
25 this invention are those of formula  $\alpha$ :



wherein:

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$X_1$  is -CH;

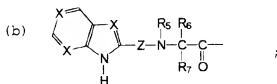
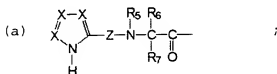
$g$  is 0 or 1;

each  $J$  is independently selected from the group consisting of -H, -OH, and -F, provided that when a  
 5 first and second  $J$  are bound to a C and said first  $J$  is -OH, said second  $J$  is -H;

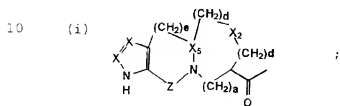
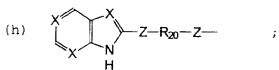
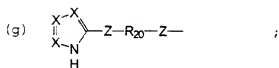
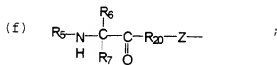
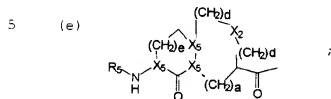
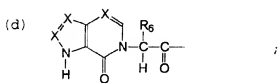
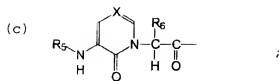
$m$  is 0, 1, or 2;

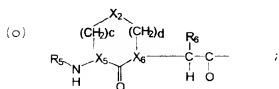
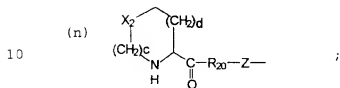
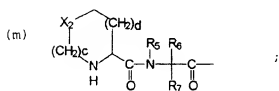
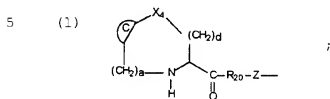
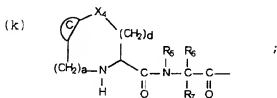
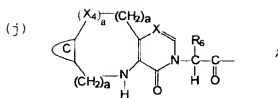
$T$  is -OH, -CO-CO<sub>2</sub>H, -CO<sub>2</sub>H, or any bioisosteric replacement for -CO<sub>2</sub>H;

10  $R_1$  is selected from the group consisting of the following formulae, in which any ring may optionally be singly or multiply substituted at any carbon by  $Q_1$ , at  
 any nitrogen by  $R_5$ , or at any atom by =O, -OH, -CO<sub>2</sub>H, or halogen; any saturated ring may optionally be  
 15 unsaturated at one or two bonds; and wherein  $R_1$  (e) and  $R_1$  (y) are optionally benzofused;



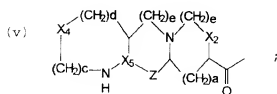
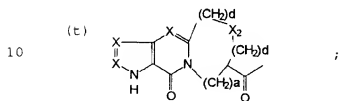
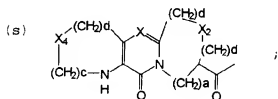
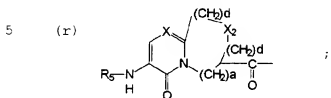
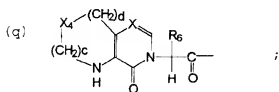
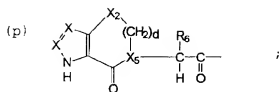
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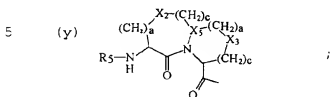
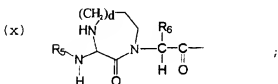
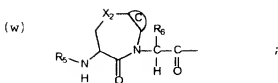




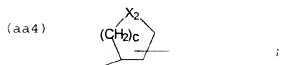
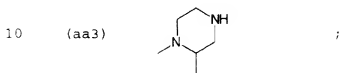
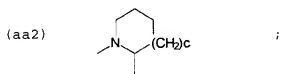
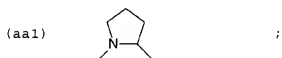
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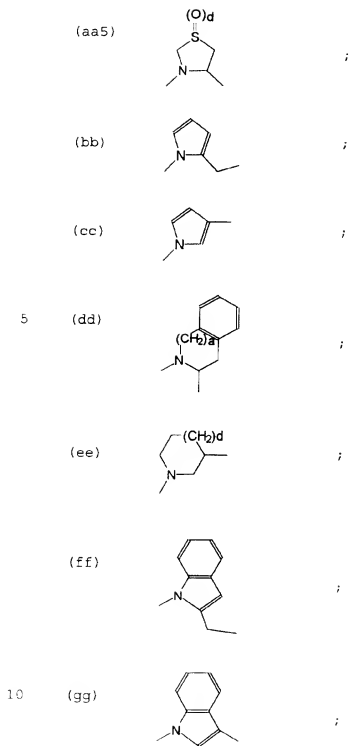
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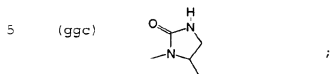
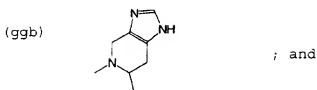
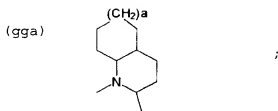
$R_{20}$  is selected from the group consisting of:



- 29 -



- 30 -



wherein each ring C is independently chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

$R_3$  is:

- CN,
- CH=CH- $R_9$ ,
- CH=N-O- $R_9$ ,
- 15 - (CH<sub>2</sub>)<sub>1-3</sub>-T<sub>1</sub>- $R_9$ ,
- CJ<sub>2</sub>- $R_9$ ,
- CO- $R_{13}$ , or
- CO-CO-N<sup>/R<sub>5</sub></sup>
- 20 \R<sub>10</sub>;

each  $R_4$  is independently selected from the group consisting of:

- H,
- Ar<sub>1</sub>,
- 25 - $R_9$ ,
- T<sub>1</sub>- $R_9$ , and

- 31 -

 $-(\text{CH}_2)_{1,2,3}-\text{T}_1-\text{R}_9;$ 

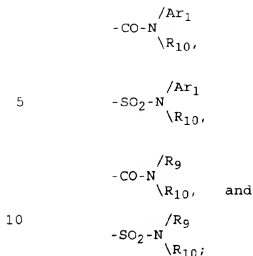
each  $\text{T}_1$  is independently selected from the group consisting of:

CH=CH-,  
5 -O-,  
-S-,  
-SO-,  
-SO<sub>2</sub>-,  
-NR<sub>10</sub>-,  
10 -NR<sub>10</sub>-CO-,  
-CO-,  
-O-CO-,  
-CO-O-,  
-CO-NR<sub>10</sub>-,  
15 -O-CO-NR<sub>10</sub>-,  
-NR<sub>10</sub>-CO-O-,  
-NR<sub>10</sub>-CO-NR<sub>10</sub>-,  
-SO<sub>2</sub>-NR<sub>10</sub>-,  
-NR<sub>10</sub>-SO<sub>2</sub>-, and  
20 -NR<sub>10</sub>-SO<sub>2</sub>-NR<sub>10</sub>-;

each  $\text{R}_5$  is independently selected from the group consisting of:

-H,  
-Ar<sub>1</sub>,  
25 -CO-Ar<sub>1</sub>,  
-SO<sub>2</sub>-Ar<sub>1</sub>,  
-CO-NH<sub>2</sub>,  
-SO<sub>2</sub>-NH<sub>2</sub>,  
-R<sub>9</sub>,  
30 -CO-R<sub>9</sub>,  
-CO-O-R<sub>9</sub>,  
-SO<sub>2</sub>-R<sub>9</sub>,

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15  $R_6$  and  $R_7$  taken together form a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-; or  $R_7$  is -H and  $R_6$  is  
 -H  
 - $Ar_1$ ,  
 - $R_9$ ,  
 - $(CH_2)_{1,2,3}\text{-T}_1\text{-R}_9$ , or  
 20 an  $\alpha$ -amino acid side chain residue;

each  $R_9$  is a  $C_{1-6}$  straight or branched alkyl group optionally singly or multiply substituted with -OH, -F, or =O and optionally substituted with one or two  $Ar_1$  groups;


25 each  $R_{10}$  is independently selected from the group consisting of -H or a  $C_{1-6}$  straight or branched alkyl group;

30 each  $R_{13}$  is independently selected from the group consisting of - $Ar_2$ , - $R_4$  and  $\begin{array}{l} \text{-N-OH} \\ \text{\R}_5; \end{array}$

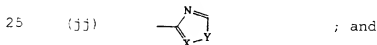
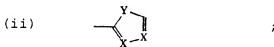
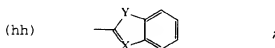
each  $Ar_1$  is a cyclic group independently selected

- 33 -

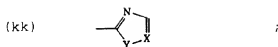
from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 15 carbon atoms and between 1 and 3 rings, said  
 5 cycloalkyl group being optionally benzofused, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocycle group containing at least one heteroatom group selected from -O-, -S-, -SO-, -SO<sub>2</sub>-, =N-, and -NH-, said heterocycle  
 10 group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted with -NH<sub>2</sub>, -CO<sub>2</sub>H, -Cl, -F, -Br, -I, -NO<sub>2</sub>, -CN,

15 =O, -OH, -perfluoro C<sub>1-3</sub> alkyl, , or -Q<sub>1</sub>;

20 each Ar<sub>2</sub> is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by -Q<sub>1</sub> and -Q<sub>2</sub>:



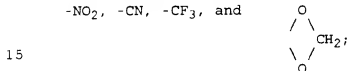
- 34 -



each  $Q_1$  is independently selected from the group consisting of:

- 5         $-Ar_1$   
           $-O-Ar_1$   
           $-R_9$ ,  
           $-T_1-R_9$ ,                      and  
           $-(CH_2)_{1,2,3}-T_1-R_9$ ;

10        each  $Q_2$  is independently selected from the group consisting of  $-OH$ ,  $-NH_2$ ,  $-CO_2H$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-I$ ,  $-NO_2$ ,  $-CN$ ,  $-CF_3$ , and



provided that when  $-Ar_1$  is substituted with a  $Q_1$  group which comprises one or more additional  $-Ar_1$  groups, said additional  $-Ar_1$  groups are not substituted with  $Q_1$ ;

20

each  $X$  is independently selected from the group consisting of  $=N-$ , and  $=CH-$ ;

each  $X_2$  is independently selected from the group consisting of  $-O-$ ,  $-CH_2-$ ,  $-NH-$ ,  $-S-$ ,  $-SO-$ , and  $-SO_2-$ ;

25        each  $X_3$  is independently selected from the group consisting of  $-CH_2-$ ,  $-S-$ ,  $-SO-$ , and  $-SO_2-$ ;

each  $X_4$  is independently selected from the group consisting of  $-CH_2-$  and  $-NH-$ ;



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each  $X_5$  is independently selected from the group  
consisting of  $-\text{CH}-$  and  $-\text{N}-$ ;

$X_6$  is  $-\text{CH}-$  or  $-\text{N}-$ ;

5 each  $Y$  is independently selected from the group  
consisting of  $-\text{O}-$ ,  $-\text{S}-$ , and  $-\text{NH}$ ;

each  $Z$  is independently  $\text{CO}$  or  $\text{SO}_2$ ;

each  $a$  is independently 0 or 1;

each  $c$  is independently 1 or 2;

10 each  $d$  is independently 0, 1, or 2; and

each  $e$  is independently 0, 1, 2, or 3;

provided that when

$R_1$  is (f),

15  $R_6$  is an  $\alpha$ -amino acid side chain residue, and

$R_7$  is  $-\text{H}$ ,

then (aa1) and (aa2) must be substituted with  $Q_1$ ;

also provided that when

20  $R_1$  is (o),

$g$  is 0,

$J$  is  $-\text{H}$ ,

$m$  is 1,

$R_6$  is an  $\alpha$ -amino acid side chain residue,

25  $R_7$  is  $-\text{H}$ ,

$X_2$  is  $-\text{CH}_2-$ ,

$X_5$  is  $-\text{CH}-$ ,

$X_6$  is  $-\text{N}-$ , and

30

$R_3$  is  $-\text{CO}-\text{N}^{\text{R}_{10}}$   
 $\backslash \text{R}_{10}$ , or  $-\text{CO}-\text{R}_{13}$ , when

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 $R_{13}$  is:

-CH<sub>2</sub>-O-CO-Ar<sub>1</sub>,  
 -CH<sub>2</sub>-S-CO-Ar<sub>1</sub>,  
 -CH<sub>2</sub>-O-Ar<sub>1</sub>,  
 -CH<sub>2</sub>-S-Ar<sub>1</sub>, or  
 -R<sub>4</sub> when -R<sub>4</sub> is -H;

then the ring of the R<sub>1</sub>(o) group must be substituted with Q<sub>1</sub> or benzofused; and

provided that when

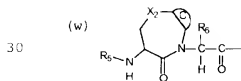
10        R<sub>1</sub> is (w),  
           g is 0,  
           J is -H,  
           m is 1,  
           T is -CO<sub>2</sub>H,  
 15        X<sub>2</sub> is O,  
           R<sub>5</sub> is benzyloxycarbonyl, and  
           ring C is benzo,

then R<sub>3</sub> cannot be -CO-R<sub>13</sub> when:

          R<sub>13</sub> is -CH<sub>2</sub>-O-Ar<sub>1</sub> and  
 20        Ar<sub>1</sub> is 1-phenyl-3-trifluoromethyl-  
           pyrazole-5-yl wherein the phenyl is optionally  
           substituted with a chlorine atom;  
           or when

          R<sub>13</sub> is -CH<sub>2</sub>-O-CO-Ar<sub>1</sub>, wherein  
 25        Ar<sub>1</sub> is 2,6-dichlorophenyl.

Preferred compounds of embodiment A employ  
 formula  $\alpha$ , wherein R<sub>1</sub> is (w):

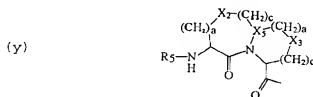


wherein the other substituents are as described

- 37 -

above.

Other preferred compounds of embodiment A employ formula  $\alpha$ , wherein  $R_1$  is (y):



5 wherein the other substituents are as described above.

More preferred compounds of embodiment A employ formula  $\alpha$ , wherein:

$X_1$  is -CH;

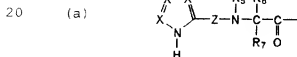
10 g is 0;

J is -H;

m is 0 or 1 and T is -CO-CO<sub>2</sub>H, or any bioisosteric replacement for -CO<sub>2</sub>H, or

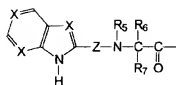
m is 1 and T is -CO<sub>2</sub>H;

15  $R_1$  is selected from the group consisting of the following formulae, in which any ring may optionally be singly or multiply substituted at any carbon by  $Q_1$ , at any nitrogen by  $R_5$ , or at any atom by =O, -OH, -CO<sub>2</sub>H, or halogen, and wherein (e) is optionally benzofused:

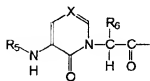


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(b)

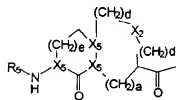


(c)

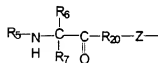


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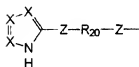
(e)



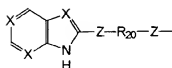
(f)



(g)

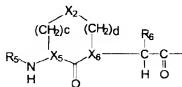


(h)

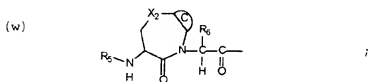
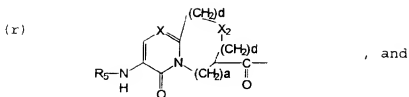


10

(o)



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5 R<sub>20</sub> is:

(aa1)



, or

(aa2)



and c is 1;

10 ring C is benzo optionally substituted with  
-C<sub>1-3</sub> alkyl, -O-C<sub>1-3</sub> alkyl, -Cl, -F or -CF<sub>3</sub>;

when R<sub>1</sub> is (a) or (b), R<sub>5</sub> is preferably -H, and

15 when R<sub>1</sub> is (c), (e), (f), (c), (r), (w), (x) or  
(y), R<sub>5</sub> is preferably:

-CO-Ar<sub>1</sub>  
-SO<sub>2</sub>-Ar<sub>1</sub>,  
-CO-NH<sub>2</sub>,  
-CO-NH-Ar<sub>1</sub>  
-CO-R<sub>9</sub>,  
-CO-O-R<sub>9</sub>,

20

- 40 -

-SO<sub>2</sub>-R<sub>9</sub>, or-CO-NH-R<sub>9</sub>,R<sub>7</sub> is -H and R<sub>6</sub> is: -H,-R<sub>9</sub>, or5 -Ar<sub>1</sub>;

R<sub>9</sub> is a C<sub>1-6</sub> straight or branched alkyl group optionally substituted with =O and optionally substituted with -Ar<sub>1</sub>;

10 R<sub>10</sub> is -H or a -C<sub>1-3</sub> straight or branched alkyl group;

Ar<sub>1</sub> is phenyl, naphthyl, pyridyl, benzothiazolyl, thienyl, benzothienyl, benzoxazolyl, 2-indanyl, or indolyl optionally substituted with -O-C<sub>1-3</sub> alkyl, -NH-C<sub>1-3</sub> alkyl, -N-(C<sub>1-3</sub> alkyl)<sub>2</sub>, -Cl, -F, -CF<sub>3</sub>,  
 15 -C<sub>1-3</sub> alkyl, or



20 Q<sub>1</sub> is R<sub>9</sub> or -(CH<sub>2</sub>)<sub>0,1,2</sub>-T<sub>1</sub>-(CH<sub>2</sub>)<sub>0,1,2</sub>-Ar<sub>1</sub>, wherein T<sub>1</sub> is -O- or -S-;

each X is independently selected from the group consisting of =N-, and =CH-;

25 each X<sub>2</sub> is independently selected from the group consisting of -O-, -CH<sub>2</sub>-, -NH-, -S-, -SO-, and -SO<sub>2</sub>-;

each X<sub>5</sub> is independently selected from the group consisting of -CH- and -N-;

30 X<sub>6</sub> is -CH- or -N-;

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provided that when:

 $R_1$  is (o), $X_2$  is  $-\text{CH}_2-$ ,

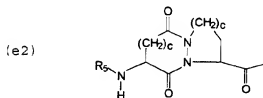
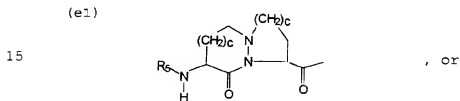
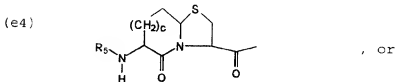
5  $X_5$  is  $-\text{CH}-$ , and  
 $\quad \quad \quad |$

$X_6$  is  $-\text{N}-$ ,  
 $\quad \quad \quad |$

10 then the ring of the  $R_1(o)$  group must be  
 substituted with  $Q_1$  or benzofused; and

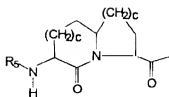
 $Z$  is  $\text{C=O}$ .

Most preferably, compounds of this more  
 preferred embodiment are those wherein the  $R_1$  group is:

and  $c$  is 2; or

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(e7)



which is optionally benzofused,  
and c is 1 or 2;

provided that when R<sub>1</sub> is (e4),

- 5           g is 0,  
           J is -H,  
           m is 1,  
           T is -CO<sub>2</sub>H,  
           R<sub>5</sub> is benzyloxycarbonyl, and  
10          c is 1,

then R<sub>3</sub> cannot be -CO-R<sub>13</sub> when

- R<sub>13</sub> is -CH<sub>2</sub>-O-Ar<sub>1</sub> and  
           Ar<sub>1</sub> is 1-phenyl-3-trifluoromethyl-pyrazole-  
15         5-yl, wherein the phenyl is optionally substituted with  
           a chlorine atom; or when

           R<sub>13</sub> is -CH<sub>2</sub>-O-CO-Ar<sub>1</sub>, wherein

           Ar<sub>1</sub> is 2,6-dichlorophenyl,

- and when the 2-position of the scaffold ring is  
20         substituted with para-fluoro-phenyl; and

also provided that when

- R<sub>1</sub> is (e7),  
           g is 0,  
           J is -H,  
25         m is 1,  
           T is CO<sub>2</sub>H or -CO-NH-OH,  
           R<sub>5</sub> is a protective group for the N atom of an  
           amino acid side chain residue, and  
           each c is 1,



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then  $R_3$  cannot be  $-\text{CO}-R_{13}$  when

$R_{13}$  is:

$-\text{CH}_2-\text{O}-\text{CO}-\text{Ar}_1$ ,

$-\text{CH}_2-\text{S}-\text{CO}-\text{Ar}_1$ ,

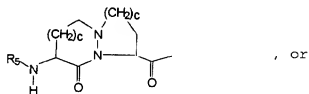
5  $-\text{CH}_2-\text{O}-\text{Ar}_1$ , or

$-\text{CH}_2-\text{S}-\text{Ar}_1$ .

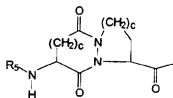
The most preferred compounds of this embodiment are those wherein:

$R_1$  is:

10 (e1)



(e2)



and  $c$  is 2;

$m$  is 1;

$T$  is  $-\text{CO}_2\text{H}$ ; and

$R_3$  is  $-\text{CO}-R_{13}$ .

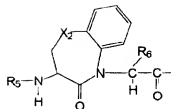
15

Other most preferred compounds of this embodiment are those wherein:

$R_1$  is:

- 44 -

(w1)



; wherein

X<sub>2</sub> is:

-O- ,  
 -S- ,  
 -SO<sub>2</sub>-, or  
 -NH-;

5

optionally substituted with R<sub>5</sub> or Q<sub>1</sub> at X<sub>2</sub> when X<sub>2</sub>  
 10 is -NH-; and

ring C is benzo substituted with -C<sub>1-3</sub> alkyl,  
 -O-C<sub>1-3</sub> alkyl, -Cl, -F or -CF<sub>3</sub>.

The ICE inhibitors of another embodiment (B)  
 of this invention are those of formula (I):

15

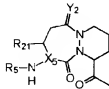
(I)



wherein:

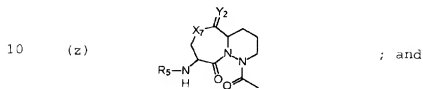
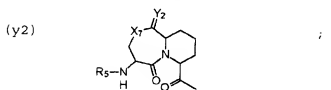
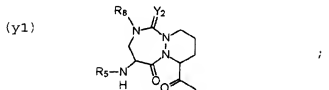
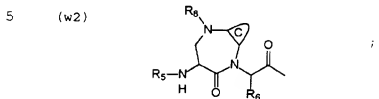
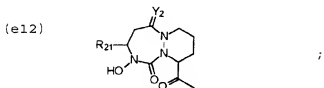
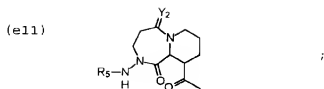
R<sub>1</sub> is selected from the group consisting of the  
 20 following formulae:

(e10)



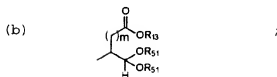
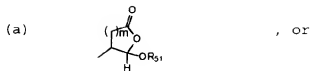
;

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ring C is chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

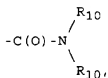
- 46 -

 $R_2$  is: $m$  is 1 or 2;

5

 $R_5$  is selected from the group consisting of: $-C(O)-R_{10}$ , $-C(O)O-R_9$ ,

10

 $-S(O)_2-R_9$ ,

15

 $-C(O)-CH_2-O-R_9$ , $-C(O)C(O)-R_{10}$ , $-R_9$ , $-H$ , and $-C(O)C(O)-OR_{10}$ ;

20

 $X_5$  is  $-\text{CH}-$  or  $-\text{N}-$ ; $Y_2$  is  $H_2$  or  $O$ ; $X_7$  is  $-\text{N}(R_8)-$  or  $-O-$ ;

25

- 47 -

$R_6$  is selected from the group consisting of -H and -CH<sub>3</sub>;

$R_8$  is selected from the group consisting of:

- 5           -C(O)- $R_{10}$ ,  
          -C(O)O- $R_9$ ,  
          -C(O)-N(H)- $R_{10}$ ,  
          -S(O)<sub>2</sub>- $R_9$ ,  
          -S(O)<sub>2</sub>-NH- $R_{10}$ ,  
10          -C(O)-CH<sub>2</sub>-OR<sub>10</sub>,  
          -C(O)C(O)- $R_{10}$ ;  
          -C(O)-CH<sub>2</sub>N( $R_{10}$ )( $R_{10}$ ),  
          -C(O)-CH<sub>2</sub>C(O)-O- $R_9$ ,  
          -C(O)-CH<sub>2</sub>C(O)- $R_9$ ,  
15          -H, and  
          -C(O)-C(O)-OR<sub>10</sub>;

          each  $R_9$  is independently selected from the group consisting of -Ar<sub>3</sub> and a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, wherein  
20          the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

          each  $R_{10}$  is independently selected from the group consisting of -H, -Ar<sub>3</sub>, a C<sub>3-6</sub> cycloalkyl group, and a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, wherein the -C<sub>1-6</sub> alkyl group is  
25          optionally unsaturated;

$R_{13}$  is selected from the group consisting of H, Ar<sub>3</sub>, and a C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, -CONH<sub>2</sub>, -OR<sub>5</sub>, -OH, -OR<sub>9</sub>, or -CO<sub>2</sub>H;

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each  $R_{51}$  is independently selected from the group consisting of  $R_9$ ,  $-C(O)-R_9$ ,  $-C(C)-N(H)-R_9$ , or each  $R_{51}$  taken together forms a saturated 4-8 member carbocyclic ring or heterocyclic ring containing  $-O-$ ,  $-S-$ , or  $-NH-$ ;

5 each  $R_{21}$  is independently selected from the group consisting of  $-H$  or a  $-C_{1-6}$  straight or branched alkyl group;

each  $Ar_3$  is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from  $-O-$ ,  $-S-$ ,  $-SO-$ ,  $SO_2$ ,  $=N-$ , and  $-NH-$ , said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

20 each  $Q_1$  is independently selected from the group consisting of  $-NH_2$ ,  $-CO_2H$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-I$ ,  $-NO_2$ ,  $-CN$ ,  $=O$ ,  $-OH$ ,  $-perfluoro\ C_{1-3}\ alkyl$ ,  $R_5$ ,  $-OR_5$ ,  $-NHR_5$ ,  $OR_9$ ,  $-NHR_9$ ,  $R_9$ ,  $-C(O)-R_{10}$ , and



30 provided that when  $-Ar_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-Ar_3$  groups, said additional  $-Ar_3$  groups are not substituted with another  $-Ar_3$ .

- 49 -

Preferably,  $R_5$  is selected from the group consisting of:

- 5        -C(O)- $R_{10}$ ,  
         -C(O)O- $R_9$ , and  
         -C(O)-NH- $R_{10}$ .

Alternatively,  $R_5$  is selected from the group consisting of:

- 10        -S(O)<sub>2</sub>- $R_9$ ,  
         -S(O)<sub>2</sub>-NH- $R_{10}$ ,  
         -C(O)-C(O)- $R_{10}$ ,  
         - $R_9$ , and  
         -C(O)-C(O)-OR<sub>10</sub>.

More preferably:

$m$  is 1;

- 15         $R_{13}$  is H or a -C<sub>1-4</sub> straight or branched alkyl group optionally substituted with -Ar<sub>3</sub>, -OH, -OR<sub>9</sub>, or -CO<sub>2</sub>H, wherein the  $R_9$  is a -C<sub>1-4</sub> branched or straight alkyl group, wherein Ar<sub>3</sub> is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q<sub>1</sub>;

- 20         $R_{21}$  is -H or -CH<sub>3</sub>;

$R_{51}$  is a C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, wherein Ar<sub>3</sub> is phenyl, optionally substituted by -Q<sub>1</sub>;

- 25        Ar<sub>3</sub> is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl;

- 50 -

each Q<sub>1</sub> is independently selected from the group consisting of -NH<sub>2</sub>, -Cl, -F, -Br, -OH, -R<sub>9</sub>, -NH-R<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or -S(O)<sub>2</sub>-R<sub>9</sub>, -OR<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub>, -OR<sub>9</sub>, -NHR<sub>9</sub>, and

5

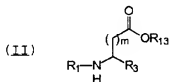


10 wherein each R<sub>9</sub> and R<sub>10</sub> are independently a -C<sub>1-6</sub>  
straight or branched alkyl group optionally substituted  
with Ar<sub>2</sub> wherein Ar<sub>2</sub> is phenyl;

provided that when  $-Ar_3$  is substituted with a  $Q_1$   
15 group which comprises one or more additional  $-Ar_3$   
groups, said additional  $-Ar_3$  groups are not substituted  
with another  $-Ar_3$ .

The ICE inhibitors of another embodiment (C) of this invention are those of formula (II):

20

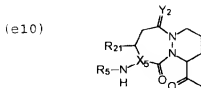


wherein:

$m$  is 1 or 2;

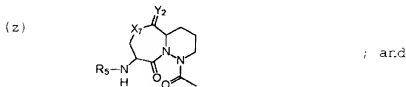
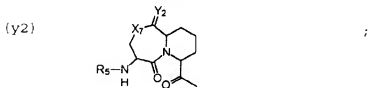
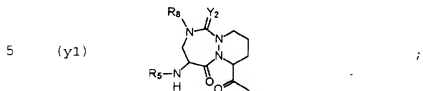
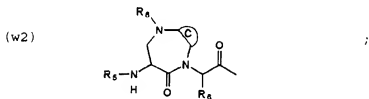
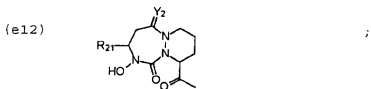
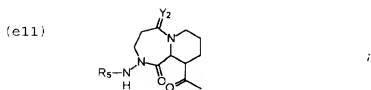
$R_1$  is selected from the group consisting of the following formulae:

25





- 51 -



10 ring C is chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

- 52 -

$R_3$  is selected from the group consisting of:

- CN,
- C(O)-H,
- C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>,
- 5        -C(O)-CH<sub>2</sub>-F,
- C=N-O-R<sub>9</sub>, and
- CO-Ar<sub>2</sub>;

$R_5$  is selected from the group consisting of:

- C(O)-R<sub>10</sub>,
- 10        -C(O)O-R<sub>9</sub>,
- $$\begin{array}{c} R_{10} \\ | \\ -C(O)-N \\ | \\ R_{10} \end{array}$$
- 15        -S(O)<sub>2</sub>-R<sub>9</sub>,
- C(O)-CH<sub>2</sub>-O-R<sub>9</sub>,
- C(O)C(O)-R<sub>10</sub>,
- 20        -R<sub>9</sub>,
- H, and
- C(O)C(O)-OR<sub>10</sub>,

25         $X_5$  is -CH- or -N-;

$$\begin{array}{c} | \\ -CH- \\ | \end{array} \quad \begin{array}{c} | \\ -N- \\ | \end{array}$$

$Y_2$  is H<sub>2</sub> or O;

$X_7$  is -N(R<sub>8</sub>)- or -O-;

each T<sub>1</sub> is independently selected from the group consisting of -O-, -S-, -S(O)-, and -S(O)<sub>2</sub>-;

30         $R_6$  is selected from the group consisting of -H and -CH<sub>3</sub>;

$R_8$  is selected from the group consisting of:

- 53 -

- 5                   -C(O)-R<sub>10</sub>,  
                  -C(O)O-R<sub>9</sub>,  
                  -C(O)-NH-R<sub>10</sub>,  
                  -S(O)<sub>2</sub>-R<sub>9</sub>,  
                  -S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
                  -C(O)-CH<sub>2</sub>-OR<sub>10</sub>,  
                  -C(O)C(O)-R<sub>10</sub>,  
                  -C(O)-CH<sub>2</sub>-N(R<sub>10</sub>)(R<sub>10</sub>),  
                  -C(O)-CH<sub>2</sub>C(O)-O-R<sub>9</sub>,  
10                  -C(O)-CH<sub>2</sub>C(O)-R<sub>9</sub>,  
                  -H, and  
                  -C(O)-C(O)-OR<sub>10</sub>;

each R<sub>9</sub> is independently selected from the group consisting of -Ar<sub>3</sub> and a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, wherein the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

each R<sub>10</sub> is independently selected from the group consisting of -H, -Ar<sub>3</sub>, a C<sub>3-6</sub> cycloalkyl group, and a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, wherein the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

each R<sub>11</sub> is independently selected from the group consisting of:

- 25                   -Ar<sub>4</sub>,  
                  -(CH<sub>2</sub>)<sub>1-3</sub>-Ar<sub>4</sub>,  
                  -H, and  
                  -C(O)-Ar<sub>4</sub>;

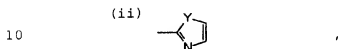
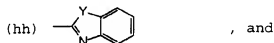
R<sub>13</sub> is selected from the group consisting of H, Ar<sub>3</sub>, and a C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, -CONH<sub>2</sub>, -OR<sub>5</sub>, -OH, -OR<sub>9</sub>, or -CO<sub>2</sub>H;

- 54 -

$-OR_{13}$  is optionally  $-N(H)-OH$ ;

each  $R_{21}$  is independently selected from the group consisting of  $-H$  or a  $-C_{1-6}$  straight or branched alkyl group;

5  $Ar_2$  is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by  $-Q_1$ :



wherein each  $Y$  is independently selected from the group consisting of  $O$  and  $S$ ;

each  $Ar_3$  is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from  $-O-$ ,  $-S-$ ,  $-SO-$ ,  $SO_2$ ,  $=N-$ , and  $-NH-$ ,  
15  $-N(R_5)-$ , and  $-N(R_6)-$  said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

25 each  $Ar_4$  is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and

- 55 -

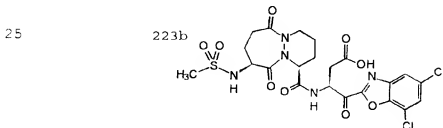
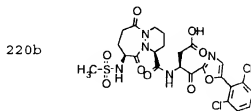
15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, -NH-, -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally  
 5 containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Q<sub>1</sub> is independently selected from the group  
 10 consisting of -NH<sub>2</sub>, -CO<sub>2</sub>H, -Cl, -F, -Br, -I, -NO<sub>2</sub>, -CN, =O, -OH, -perfluoro C<sub>1-3</sub> alkyl, R<sub>5</sub>, -OR<sub>5</sub>, -NHR<sub>5</sub>, OR<sub>9</sub>, -NHR<sub>9</sub>, R<sub>9</sub>, -C(O)-R<sub>10</sub>, and

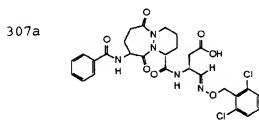
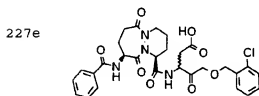
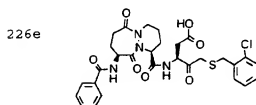
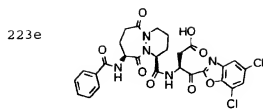


provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub>  
 20 group which comprises one or more additional -Ar<sub>3</sub> with another -Ar<sub>3</sub>.

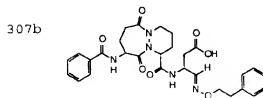
Preferred compounds of this embodiment include, but are not limited to:



- 56 -

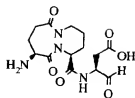


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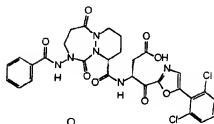


- 57 -

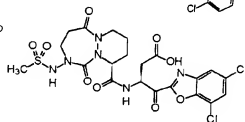
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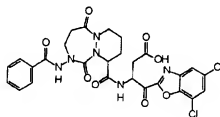
820b



823b

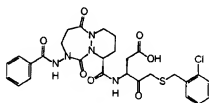


823e

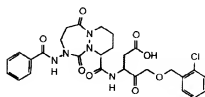


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826e

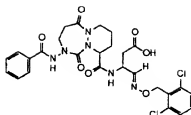


827e

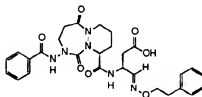


- 58 -

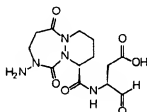
907a



907b



1029



Preferred compounds of embodiment C employ  
 5 formula (II), wherein  $R_1$  is (e11) and the other  
 substituents are as defined above.

Other preferred compounds of embodiment C  
 employ formula (II), wherein  $R_1$  is (e12) and the other  
 substituents are as defined above.

10 Other preferred compounds of embodiment C  
 employ formula (II) wherein  $R_1$  is (y1) and the other  
 substituents are as defined above.

Other preferred compounds of embodiment C  
 15 employ formula (II) wherein  $R_1$  is (y2) and the other  
 substituents are as defined above.



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Other preferred compounds of embodiment C of  
employ formula (II) wherein  $R_1$  is (z) and the other  
substituents are as defined above.

Other preferred compound of embodiment C  
5 employ formula (II) wherein  $R_1$  is (w2) and the other  
substituents are as defined above.

More preferably,  $R_1$  is (w2) and

m is 1;

ring C is benzo, pyrido, or thieno;

10  $R_3$  is selected from the group consisting of  $-C(O)-$   
H,  $-C(O)-Ar_2$ , and  $-C(O)CH_2-T_1-R_{11}$ ;

$R_5$  is selected from the group consisting of:

$-C(O)-R_{10}$ , wherein  $R_{10}$  is  $-Ar_3$ ;

$-C(O)O-R_9$ , wherein  $R_9$  is  $-CH_2-Ar_3$ ;

15  $-C(O)C(O)-R_{10}$ , wherein  $R_{10}$  is  $-CH_2Ar_3$ ;

$-R_9$ , wherein  $R_9$  is a  $C_{1-2}$  alkyl group  
substituted with  $-Ar_3$ ; and

$-C(O)C(O)-OR_{10}$ , wherein  $R_{10}$  is  $-CH_2Ar_3$ ;

20  $T_1$  is O or S;

$R_6$  is H;

$R_8$  is selected from the group consisting  $-C(O)-R_{10}$ ,  
 $-C(O)-CH_2-OR_{10}$ , and  $-C(O)CH_2-N(R_{10})(R_{10})$ , wherein  $R_{10}$  is  
H,  $CH_3$ , or  $-CH_2CH_3$ ;

25  $R_{11}$  is selected from the group consisting of  $-Ar_4$ ,  
 $-(CH_2)_{1-3}-Ar_4$ , and  $-C(O)-Ar_4$ ;

- 60 -

$R_{13}$  is H or a  $-C_{1-4}$  straight or branched alkyl group optionally substituted with  $-Ar_3$ ,  $-OH$ ,  $-OR_9$ , or  $-CO_2H$ , wherein the  $R_9$  is a  $-C_{1-4}$  branched or straight alkyl group, wherein  $Ar_3$  is morpholinyl or phenyl,  
 5 wherein the phenyl is optionally substituted with  $Q_1$ ;

$Ar_2$  is (hh);

$Y$  is O;

$Ar_3$  is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, thiazolyl, benzimidazolyl,  
 10 thienothienyl, thiadiazolyl, benzotriazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl;

$Ar_4$  is phenyl, tetrazolyl, naphthyl, pyridinyl, oxazolyl, pyrimidinyl, or indolyl;

15 each  $Q_1$  is independently selected from the group consisting of  $-NH_2$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-OH$ ,  $-R_9$ ,  $-NH-R_5$  wherein  $R_5$  is  $-C(O)-R_{10}$  or  $-S(O)_2-R_9$ ,  $-OR_5$  wherein  $R_5$  is  $-C(O)-R_{10}$ ,  $-OR_9$ ,  $-NHR_9$ , and



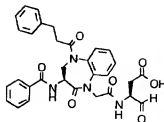
wherein each  $R_9$  and  $R_{10}$  are independently a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$  wherein  $Ar_3$  is phenyl;

provided that when  $-Ar_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-Ar_3$   
 30 groups, said additional  $-Ar_3$  groups are not substituted with another  $-Ar_3$ .

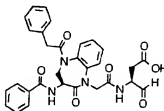
- 61 -

Preferred compounds of this embodiment include, but are not limited to:

605a

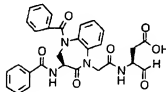


605b

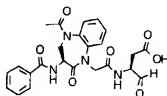


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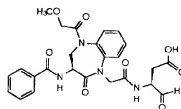
605c



605d

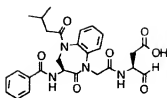


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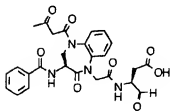


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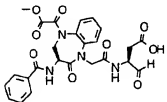
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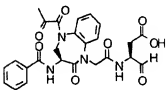
605g



605h

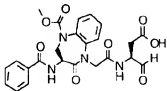


605i



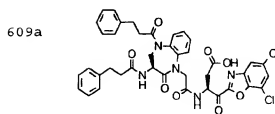
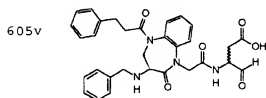
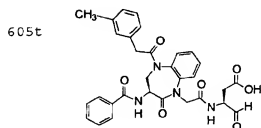
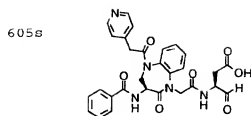
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605j

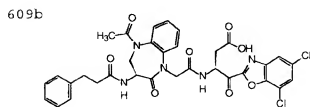




- 64 -

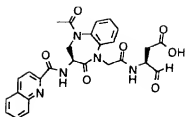


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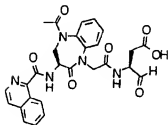


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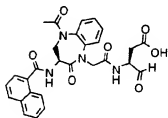
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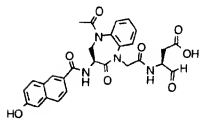
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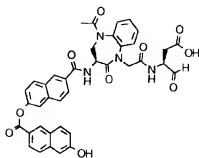
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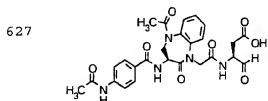
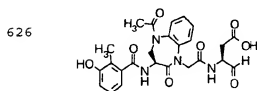
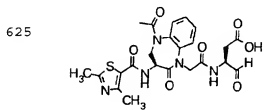
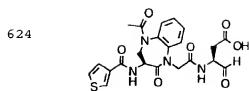
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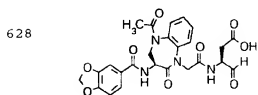
623



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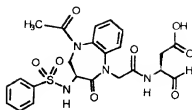
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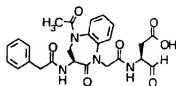


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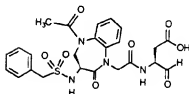
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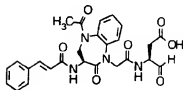
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631

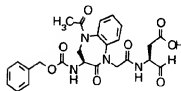


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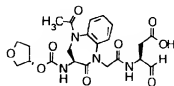


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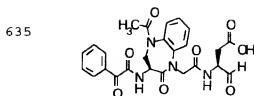
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Other preferred compounds of embodiment C  
employ formula (II) wherein  $R_1$  is (e10),  $X_5$  is CH, and  
5 the other substituents are as defined above.

More preferred compounds of embodiment C  
employ formula (II) wherein  $R_1$  is (e10),  $X_5$  is CH,  $R_3$  is  
CO-Ar<sub>2</sub>, and the other substituents are as defined  
above.

10 Other more preferred compounds of embodiment  
C employ formula (II) wherein  $R_1$  is (e10),  $X_5$  is CH,  $R_3$   
is -C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>,  $R_{11}$  is -(CH<sub>2</sub>)<sub>1-3</sub>-Ar<sub>4</sub>, and the other  
substituents are as defined above.

Other more preferred compounds of embodiment  
15 C employ formula (II) wherein  $R_1$  is (e10) and  $X_5$  is CH  
and

$R_3$  is -C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>;

T<sub>1</sub> is O; and

R<sub>11</sub> is -C(O)-Ar<sub>4</sub>,

20 and the other substituents are as defined above.

More preferably, in these more preferred compounds,  $R_5$   
is selected from the group consisting of:

-C(O)-R<sub>10</sub>,

-C(O)O-R<sub>9</sub>, and

25 -C(O)-NH-R<sub>10</sub>.

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Alternatively, in these more preferred compounds,  $R_5$  is selected from the group consisting of:

- 5            $-S(O)_2-R_9$ ,  
           $-S(O)_2-NH-R_{10}$ ,  
           $-C(O)-C(O)-R_{10}$ ,  
           $-R_9$ , and  
           $-C(O)-C(O)-OR_{10}$ .

Most preferably, in these more preferred compounds,

- 10            $m$  is 1;  
           $T_1$  is O or S;

- 15            $R_{13}$  is H or a  $-C_{1-4}$  straight or branched alkyl group optionally substituted with  $-Ar_3$ ,  $-OH$ ,  $-OR_9$ , or  $-CO_2H$ , wherein the  $R_9$  is a  $-C_{1-4}$  branched or straight alkyl group, wherein  $Ar_3$  is morpholinyl or phenyl, wherein the phenyl is optionally substituted with  $Q_1$ ;

$R_{21}$  is  $-H$  or  $-CH_3$ ;

- 20            $R_{51}$  is a  $C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$ , wherein  $Ar_3$  is phenyl, optionally substituted by  $-Q_1$ ;

$Ar_2$  is (hh);

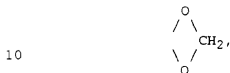
$Y$  is O, and

- 25            $Ar_3$  is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl;

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Ar<sub>4</sub> is phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl;

each Q<sub>1</sub> is independently selected from the group consisting of -NH<sub>2</sub>, -Cl, -F, -Br, -OH, -R<sub>9</sub>, -NH-R<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or -S(O)<sub>2</sub>-R<sub>9</sub>, -OR<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub>, -OR<sub>9</sub>, -NHR<sub>9</sub>, and



wherein each R<sub>9</sub> and R<sub>10</sub> are independently a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub> wherein Ar<sub>3</sub> is phenyl;

provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub> group which comprises one or more additional -Ar<sub>3</sub> groups, said additional -Ar<sub>3</sub> groups are not substituted with another -Ar<sub>3</sub>.

Other more preferred compounds of embodiment C employ formula (II) wherein R<sub>1</sub> is (e10), X<sub>5</sub> is CH, R<sub>3</sub> is -C(O)-H, and the other substituents are as defined above.

More preferably, in these more preferred compounds, R<sub>5</sub> is selected from the group consisting of:

-C(O)-R<sub>10</sub>,  
-C(O)O-R<sub>9</sub>, and  
-C(O)-NH-R<sub>10</sub>.

Alternatively, in these more preferred compounds, R<sub>5</sub> is selected from the group consisting of:

-S(O)<sub>2</sub>-R<sub>9</sub>,  
-S(O)<sub>2</sub>-NH-R<sub>10</sub>.

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-C(O)-C(O)-R<sub>10</sub>,  
-R<sub>9</sub>, and  
-C(O)-C(O)-OR<sub>10</sub>.

Most preferably, in these more preferred compounds,

5           m is 1;

T<sub>1</sub> is O or S;

10           R<sub>13</sub> is H or a -C<sub>1-4</sub> straight or branched alkyl group optionally substituted with -Ar<sub>3</sub>, -OH, -OR<sub>9</sub>, or -CO<sub>2</sub>H, wherein the R<sub>9</sub> is a -C<sub>1-4</sub> branched or straight alkyl group, wherein Ar<sub>3</sub> is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q<sub>1</sub>;

R<sub>21</sub> is -H or -CH<sub>3</sub>;

15           R<sub>51</sub> is a C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, wherein Ar<sub>3</sub> is phenyl, optionally substituted by -Q<sub>1</sub>;

Ar<sub>2</sub> is (hh);

Y is O, and

20           Ar<sub>3</sub> is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl benzofuranyl, and indolyl;

25           Ar<sub>4</sub> is phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl;

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each  $Q_1$  is independently selected from the group consisting of  $-\text{NH}_2$ ,  $-\text{Cl}$ ,  $-\text{F}$ ,  $-\text{Br}$ ,  $-\text{OH}$ ,  $-\text{R}_9$ ,  $-\text{NH}-\text{R}_5$  wherein  $\text{R}_5$  is  $-\text{C}(\text{O})-\text{R}_{10}$  or  $-\text{S}(\text{O})_2-\text{R}_9$ ,  $-\text{OR}_5$  wherein  $\text{R}_5$  is  $-\text{C}(\text{O})-\text{R}_{10}$ ,  $-\text{OR}_9$ ,  $-\text{NHR}_9$ , and

5



10 wherein each  $\text{R}_9$  and  $\text{R}_{10}$  are independently a  $-\text{C}_{1-6}$  straight or branched alkyl group optionally substituted with  $\text{Ar}_3$  wherein  $\text{Ar}_3$  is phenyl;

15 provided that when  $-\text{Ar}_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-\text{Ar}_3$  groups, said additional  $-\text{Ar}_3$  groups are not substituted with another  $-\text{Ar}_3$ ,

20 Other more preferred compounds of embodiment C employ formula (II) wherein  $\text{R}_1$  is (e10) and  $\text{X}_5$  is  $\text{CH}$ ,  $\text{R}_3$  is  $-\text{CO}-\text{CH}_2-\text{T}_1-\text{R}_{11}$ , and  $\text{R}_{11}$  is  $-\text{Ar}_4$ , and the other substituents are as defined above.

More preferably, in these more preferred compounds,  $\text{R}_5$  is selected from the group consisting of:

25  $-\text{C}(\text{O})-\text{R}_{10}$ ,  
 $-\text{C}(\text{O})\text{O}-\text{R}_9$ , and  
 $-\text{C}(\text{O})-\text{NH}-\text{R}_{10}$ .

Alternatively, in these more preferred compounds,  $\text{R}_5$  is selected from the group consisting of:

$-\text{S}(\text{O})_2-\text{R}_9$ ,

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-S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
-C(O)-C(O)-R<sub>10</sub>,  
-R<sub>9</sub>, and  
-C(O)-C(O)-OR<sub>10</sub>.

- 5 Most preferably, in these more preferred compounds,
- m is 1;
- T<sub>1</sub> is O or S;
- 10 R<sub>13</sub> is H or a -C<sub>1-4</sub> straight or branched alkyl group optionally substituted with -Ar<sub>3</sub>, -OH, -OR<sub>9</sub>, or -CO<sub>2</sub>H, wherein the R<sub>9</sub> is a -C<sub>1-4</sub> branched or straight alkyl group, wherein Ar<sub>3</sub> is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q<sub>1</sub>;
- R<sub>21</sub> is -H or -CH<sub>3</sub>;
- 15 R<sub>51</sub> is a C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, wherein Ar<sub>3</sub> is phenyl, optionally substituted by -Q<sub>1</sub>;
- Ar<sub>2</sub> is (hh);
- Y is O, and
- 20 Ar<sub>3</sub> is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[blthiophenyl, pyridyl
- 25 benzofuranyl, and indolyl;
- Ar<sub>4</sub> is phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl;

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each  $Q_1$  is independently selected from the group consisting of  $-NH_2$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-OH$ ,  $-R_9$ ,  $-NH-R_5$  wherein  $R_5$  is  $-C(O)-R_{10}$  or  $-S(O)_2-R_9$ ,  $-OR_5$  wherein  $R_5$  is  $-C(O)-R_{10}$ ,  $-OR_9$ ,  $-NHR_9$ , and



10 wherein each  $R_9$  and  $R_{10}$  are independently a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$  wherein  $Ar_3$  is phenyl;

15 provided that when  $-Ar_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-Ar_3$  groups, said additional  $-Ar_3$  groups are not substituted with another  $-Ar_3$ .

20 Other preferred compounds of embodiment C employ formula (II) wherein  $R_1$  is (e10),  $X_5$  is N, and the other substituents are as defined above.

More preferred compounds of embodiment C, employ formula (II) wherein  $R_1$  is (e10),  $X_5$  is N,  $R_3$  is  $CO-Ar_2$ , and the other substituents are as defined above.

25 Other more preferred compounds of embodiment C, employ formula (II) wherein  $R_1$  is (e10),  $X_5$  is N,  $R_3$  is  $-C(O)-CH_2-T_1-R_{11}$ ,  $R_{11}$  is  $-(CH_2)_{1-3}-Ar_4$ , and the other substituents are as defined above.

30 Other more preferred compounds of embodiment C, employ formula (II) wherein  $R_1$  is (e10) and  $X_5$  is N and:



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$R_3$  is  $-C(O)-CH_2-T_1-R_{11}$ ;

$T_1$  is O; and

$R_{11}$  is  $-C(O)-Ar_4$ , and the other substituents are as defined above.

- 5 More preferably, in these more preferred compounds,  $R_5$  is selected from the group consisting of:

$-C(O)-R_{10}$ ,

$-C(O)O-R_9$ , and

$-C(O)-NH-R_{10}$ .

- 10 Alternatively, in these more preferred compounds,  $R_5$  is selected from the group consisting of:

$-S(O)_2-R_9$ ,

$-S(O)_2-NH-R_{10}$ ,

$-C(O)-C(O)-R_{10}$ ,

- 15  $-R_9$ , and

$-C(O)-C(O)-OR_{10}$ .

Most preferably, in these more preferred compounds,  $R_5$  is selected from the group consisting of:

$-S(O)_2-R_9$ ,

- 20  $-S(O)_2-NH-R_{10}$ ,

$-C(O)-C(O)-R_{10}$ ,

$-R_9$ , and

$-C(O)-C(O)-OR_{10}$ .

$m$  is 1;

25

$T_1$  is O or S;

$R_{13}$  is H or a  $-C_{1-4}$  straight or branched alkyl group optionally substituted with  $-Ar_3$ ,  $-OH$ ,  $-OR_9$ , or  $-CO_2H$ , wherein the  $R_9$  is a  $-C_{1-4}$  branched or straight

30

alkyl group, wherein  $Ar_3$  is morpholinyl or phenyl, wherein the phenyl is optionally substituted with  $Q_1$ ;

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$R_{21}$  is -H or  $-CH_3$ ;

$R_{51}$  is a  $C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$ , wherein  $Ar_3$  is phenyl, optionally substituted by  $-Q_1$ ;

5  $Ar_2$  is (hh);

$Y$  is O, and

$Ar_3$  is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl benzofuranyl, and indolyl;

$Ar_4$  is phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl;

15 each  $Q_1$  is independently selected from the group consisting of  $-NH_2$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-OH$ ,  $-R_9$ ,  $-NH-R_5$  wherein  $R_5$  is  $-C(O)-R_{10}$  or  $-S(O)_2-R_9$ ,  $-OR_5$  wherein  $R_5$  is  $-C(O)-R_{10}$ ,  $-OR_9$ ,  $-NHR_9$ , and



wherein each  $R_9$  and  $R_{10}$  are independently a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$  wherein  $Ar_3$  is phenyl;

provided that when  $-Ar_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-Ar_3$  groups, said additional  $-Ar_3$  groups are not substituted with another  $-Ar_3$ .

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Other more preferred compounds of embodiment C, employ formula (II) wherein  $R_1$  is (e10),  $X_5$  is N,  $R_3$  is -C(O)-H, and the other substituents are as defined above.

- 5 More preferably, in these more preferred compounds,  $R_5$  is selected from the group consisting of:
- C(O)- $R_{10}$ ,
  - C(O)O- $R_9$ , and
  - C(O)-NH- $R_{10}$ .
- 10 Alternatively, in these more preferred compounds,  $R_5$  is selected from the group consisting of:
- S(O)<sub>2</sub>- $R_9$ ,
  - S(O)<sub>2</sub>-NH- $R_{10}$ ,
  - C(O)-C(O)- $R_{10}$ ,
  - 15 - $R_9$ , and
  - C(O)-C(O)-OR<sub>10</sub>.

Most preferably, in these more preferred compounds,

$m$  is 1;

- 20  $T_1$  is O or S;

- $R_{13}$  is H or a -C<sub>1-4</sub> straight or branched alkyl group optionally substituted with -Ar<sub>3</sub>, -OH, -OR<sub>9</sub>, or -CO<sub>2</sub>H, wherein the  $R_9$  is a -C<sub>1-4</sub> branched or straight alkyl group, wherein Ar<sub>3</sub> is morpholinyl or phenyl,
- 25 wherein the phenyl is optionally substituted with Q<sub>1</sub>;

$R_{21}$  is -H or -CH<sub>3</sub>;

$R_{51}$  is a C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, wherein Ar<sub>3</sub> is phenyl, optionally substituted by -Q<sub>1</sub>;

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Ar<sub>2</sub> is (hh);

Y is O, and

Ar<sub>3</sub> is phenyl, naphthyl, thienyl, quinolinyl,  
5 isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl,  
benzotriazolyl, benzimidazolyl, thienothienyl,  
imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl  
benzofuranyl, and indolyl;

Ar<sub>4</sub> is phenyl, tetrazolyl, pyridinyl, oxazolyl,  
10 naphthyl, pyrimidinyl, or thienyl;

each Q<sub>1</sub> is independently selected from the group  
consisting of -NH<sub>2</sub>, -Cl, -F, -Br, -OH, -R<sub>9</sub>, -NH-R<sub>5</sub>  
wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or -S(O)<sub>2</sub>-R<sub>9</sub>, -OR<sub>5</sub> wherein R<sub>5</sub> is  
15 -C(O)-R<sub>10</sub>, -OR<sub>9</sub>, -NHR<sub>9</sub>, and



20 wherein each R<sub>9</sub> and R<sub>10</sub> are independently a -C<sub>1-6</sub>  
straight or branched alkyl group optionally substituted  
with Ar<sub>3</sub> wherein Ar<sub>3</sub> is phenyl;

provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub>  
25 group which comprises one or more additional -Ar<sub>3</sub>  
groups, said additional -Ar<sub>3</sub> groups are not substituted  
with another -Ar<sub>3</sub>.

Other more preferred compounds of embodiment  
C, employ formula (II) wherein R<sub>1</sub> is (e10), X<sub>5</sub> is N, R<sub>3</sub>  
30 is -CO-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>, R<sub>11</sub> is -Ar<sub>4</sub>, and the other  
substituents are as defined above.

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More preferably, in these more preferred compounds,  $R_5$  is selected from the group consisting of:

- 5            $-C(O)-R_{10}$ ,  
             $-C(O)O-R_9$ , and  
             $-C(O)-NH-R_{10}$ .

Alternatively, in these more preferred compounds,  $R_5$  is selected from the group consisting of:

- 10            $-S(O)_2-R_9$ ,  
             $-S(O)_2-NH-R_{10}$ ,  
             $-C(O)-C(O)-R_{10}$ ,  
             $-R_9$ , and  
             $-C(O)-C(O)-OR_{10}$ .

Most preferably, in these more preferred compounds

- 15           m is 1;  
  
             $T_1$  is O or S;

- $R_{13}$  is H or a  $-C_{1-4}$  straight or branched alkyl group optionally substituted with  $-Ar_3$ ,  $-OH$ ,  $-OR_9$ , or  $-CO_2H$ , wherein the  $R_9$  is a  $-C_{1-4}$  branched or straight  
20           alkyl group, wherein  $Ar_3$  is morpholinyl or phenyl, wherein the phenyl is optionally substituted with  $Q_1$ ;

$R_{21}$  is  $-H$  or  $-CH_3$ ;

- $R_{51}$  is a  $C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$ , wherein  $Ar_3$  is phenyl,  
25           optionally substituted by  $-Q_1$ ;

$Ar_2$  is (hh);

            Y is O, and

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Ar<sub>3</sub> is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl;

Ar<sub>4</sub> is phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl;

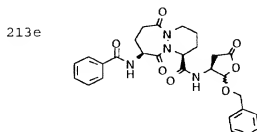
each Q<sub>1</sub> is independently selected from the group consisting of -NH<sub>2</sub>, -Cl, -F, -Br, -OH, -R<sub>9</sub>, -NH-R<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or -S(O)<sub>2</sub>-R<sub>9</sub>, -OR<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub>, -OR<sub>9</sub>, -NHR<sub>9</sub>, and



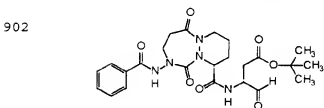
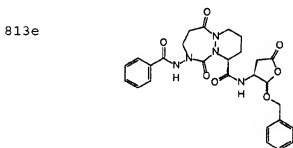
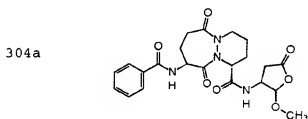
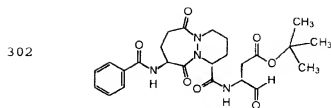
wherein each R<sub>9</sub> and R<sub>10</sub> are independently a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub> wherein Ar<sub>3</sub> is phenyl;

provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub> group which comprises one or more additional -Ar<sub>3</sub> groups, said additional -Ar<sub>3</sub> groups are not substituted with another -Ar<sub>3</sub>.

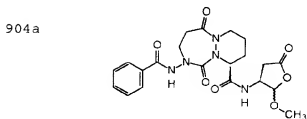
Preferred compounds of embodiment B include, but are not limited to:



- 81 -

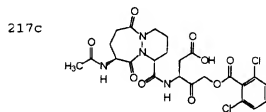
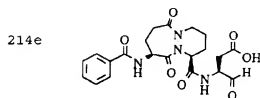
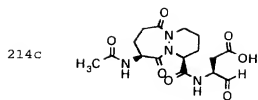


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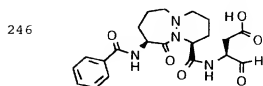
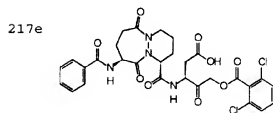
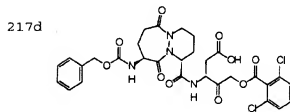


Preferred compounds of embodiment C include, but are not limited to:

- 82 -

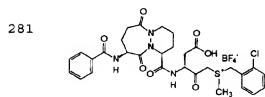
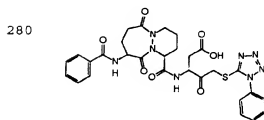
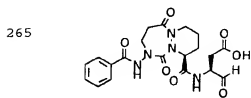
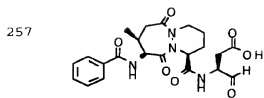


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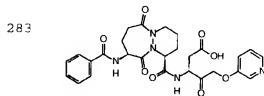
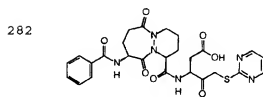




- 83 -

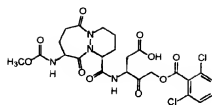


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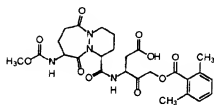


- 84 -

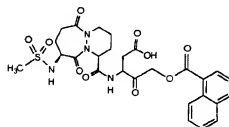
284



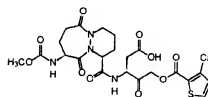
285



286

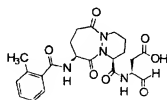


287

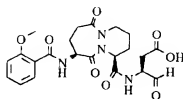


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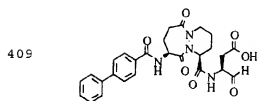
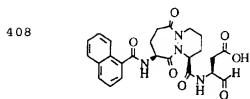
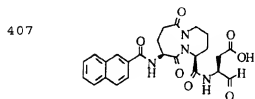
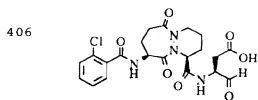
404



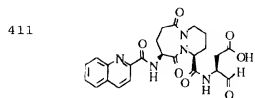
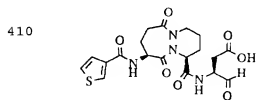
405



- 85 -

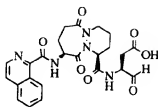


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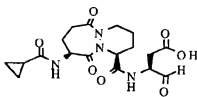


- 86 -

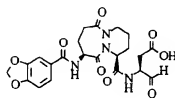
412



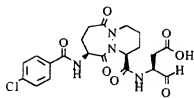
413



415

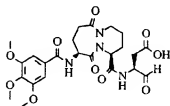


416

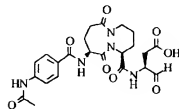


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417

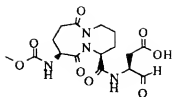


418

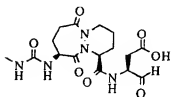


- 87 -

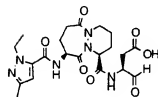
419



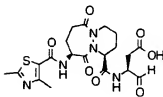
420



422

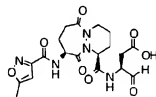


423

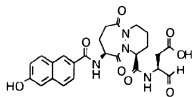


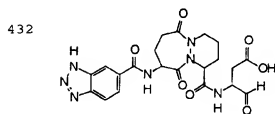
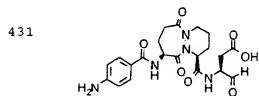
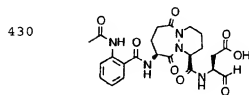
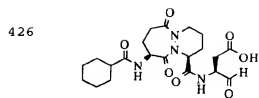
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424

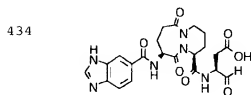
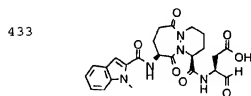


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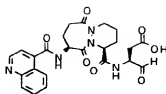


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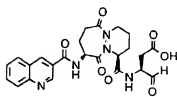


- 89 -

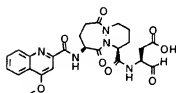
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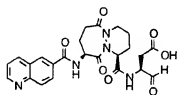
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437

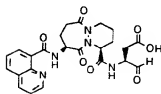


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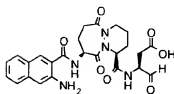


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439

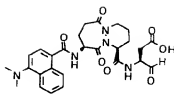


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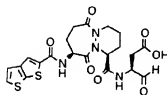


- 90 -

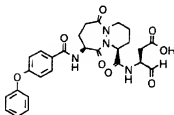
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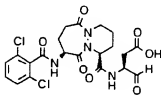
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443

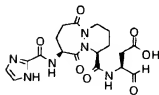


444



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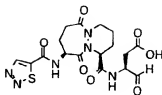
445



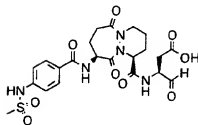


- 91 -

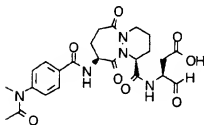
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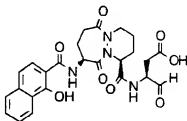
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448

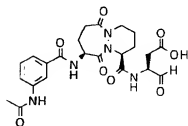


449

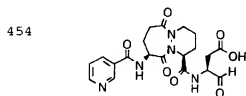
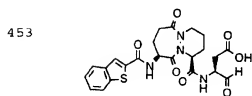
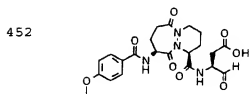
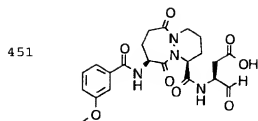


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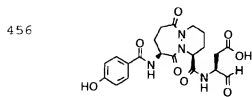
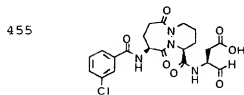
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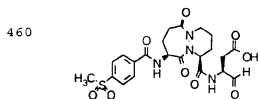
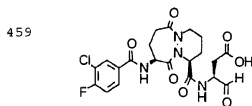
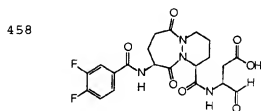
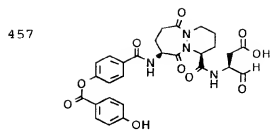
- 92 -



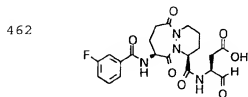
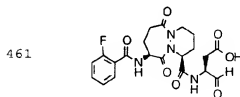
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- 93 -

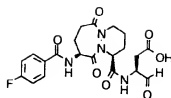


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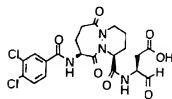


- 94 -

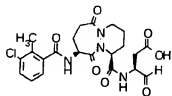
463



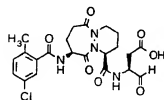
464



465

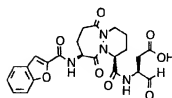


466

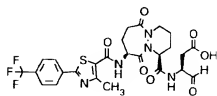


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467

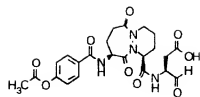


468

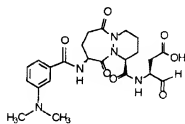


- 95 -

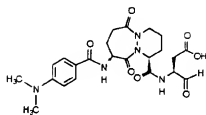
469



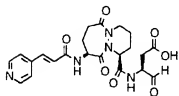
470



471

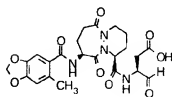


472



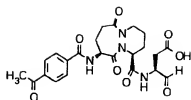
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473

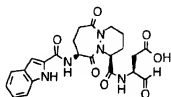


- 96 -

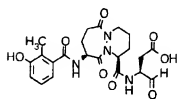
474



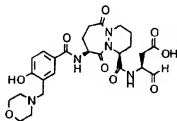
475



476

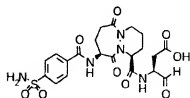


477



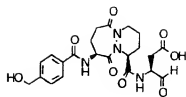
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478

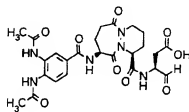


- 97 -

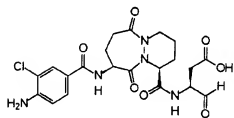
479



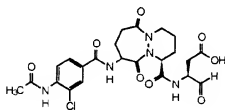
480



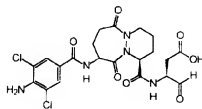
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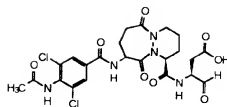
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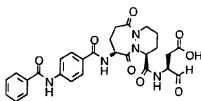
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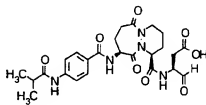
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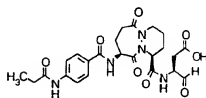
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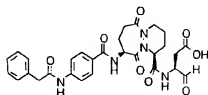


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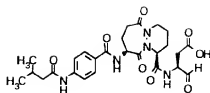
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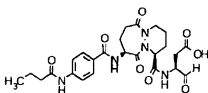


- 99 -

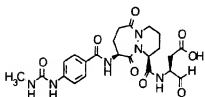
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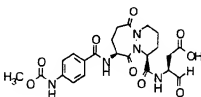
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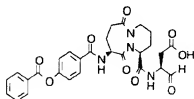


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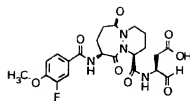
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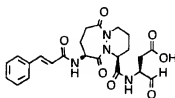


- 100 -

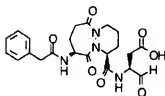
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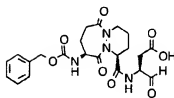
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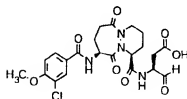


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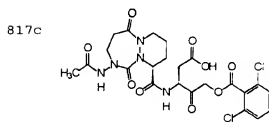
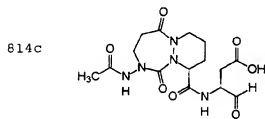
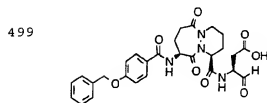
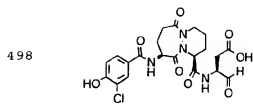


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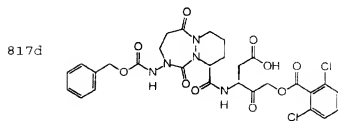
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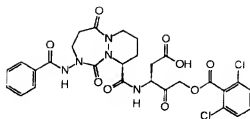


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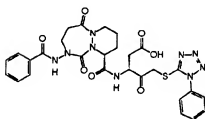


- 102 -

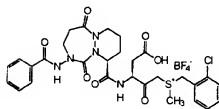
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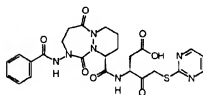
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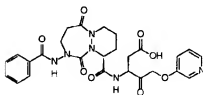


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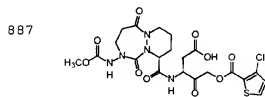
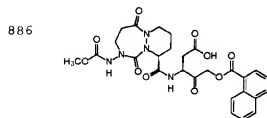
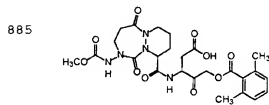
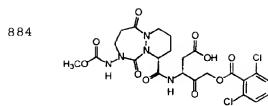


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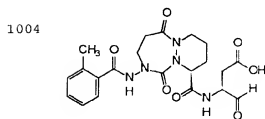
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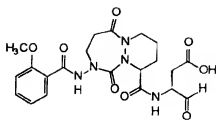


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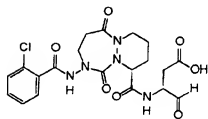


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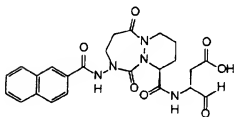
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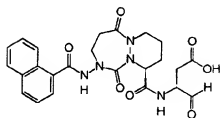
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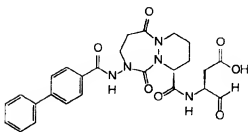


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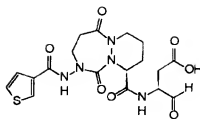
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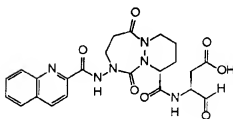


- 105 -

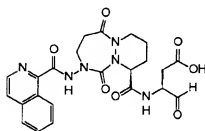
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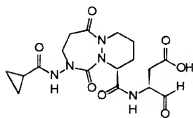
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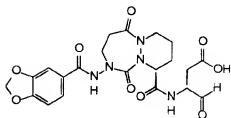


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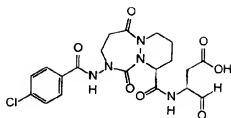
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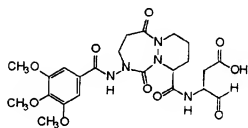


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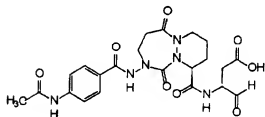
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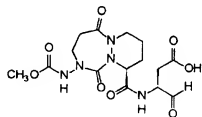
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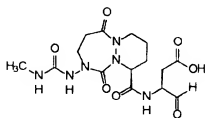


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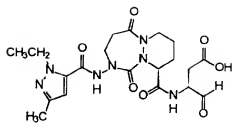
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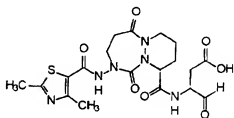


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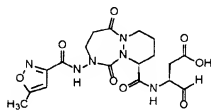
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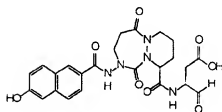
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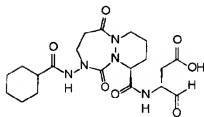


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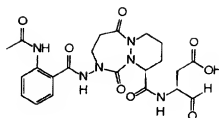
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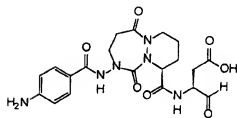


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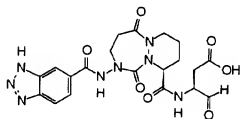
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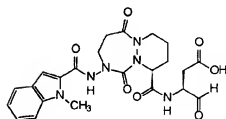
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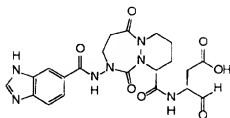


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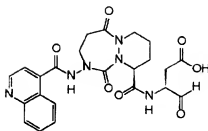
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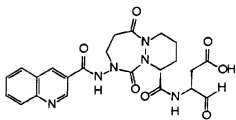


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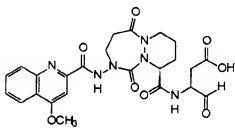
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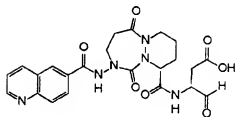
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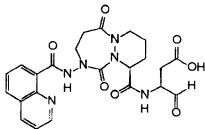


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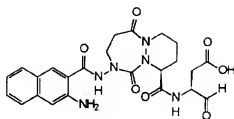
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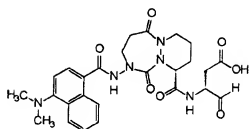


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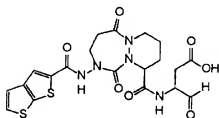
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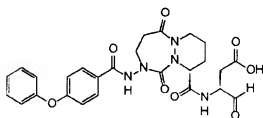
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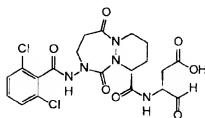


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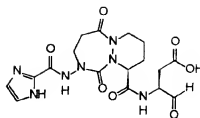
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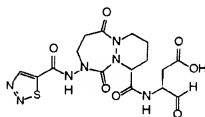


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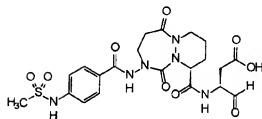
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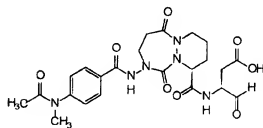
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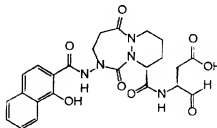


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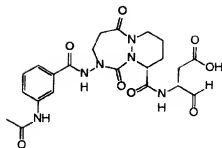
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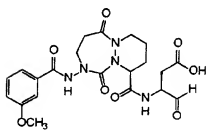


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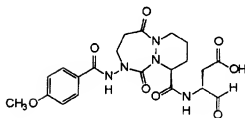
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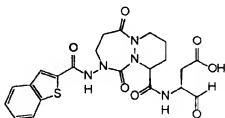
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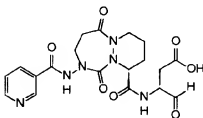


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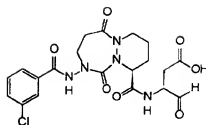
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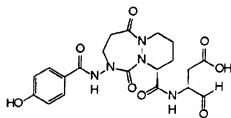


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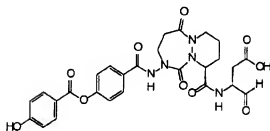
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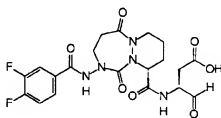
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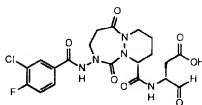


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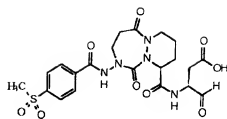
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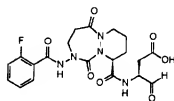


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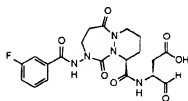
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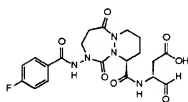
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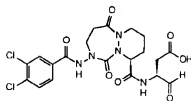


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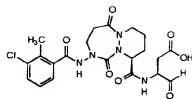
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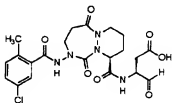


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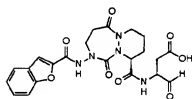
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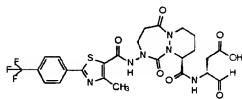
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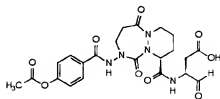


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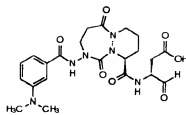
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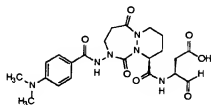


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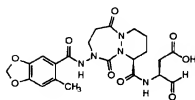
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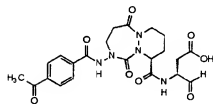
1071



1073

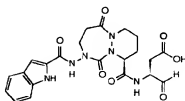


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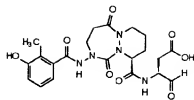
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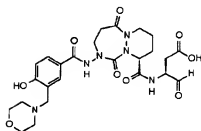


- 117 -

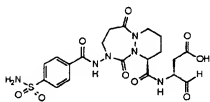
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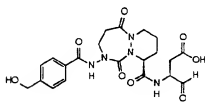
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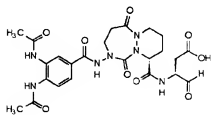
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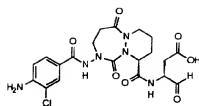


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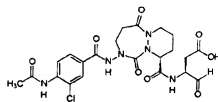


- 118 -

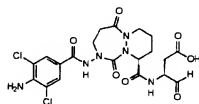
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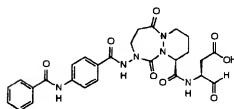
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1082

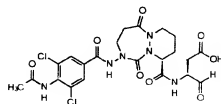


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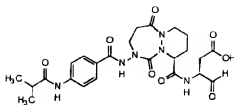
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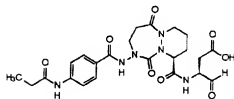


- 119 -

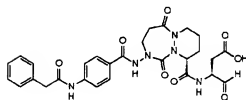
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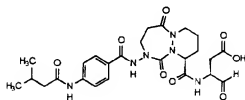
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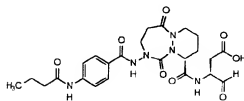


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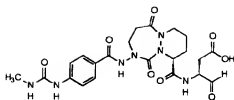
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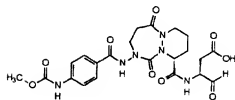


- 120 -

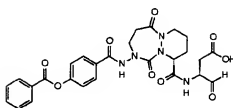
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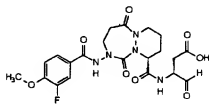
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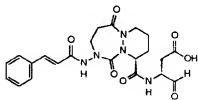


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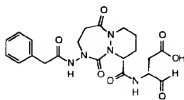


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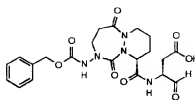


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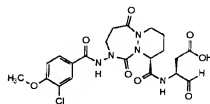


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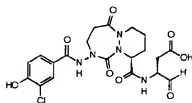
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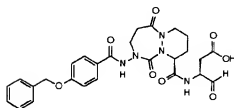
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1098

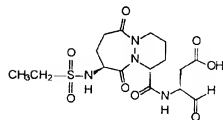


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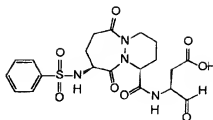
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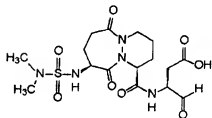


- 122 -

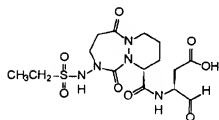
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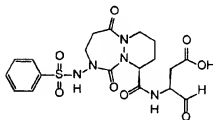
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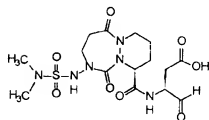
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1027



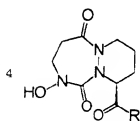
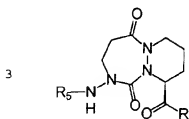
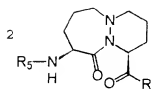
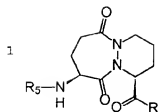
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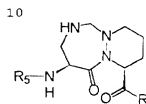
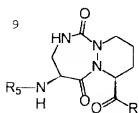
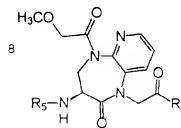
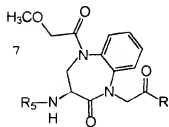
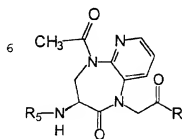
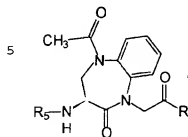
Specific compounds of this invention also include, but are not limited to, those compounds whose structures comprise scaffolds 1-22:



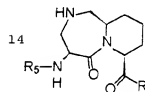
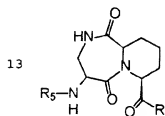
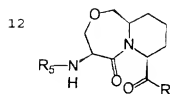
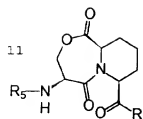
- 123 -



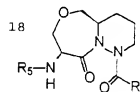
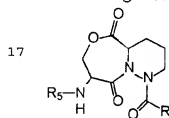
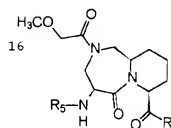
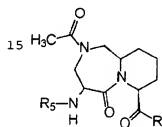
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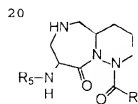
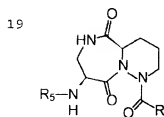
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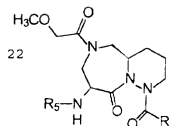
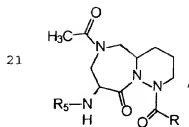
5



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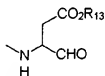


wherein:

R is



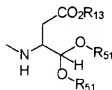
5



, wherein


R<sub>13</sub> is -CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CH(CH<sub>3</sub>)(CH<sub>3</sub>),  
-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>-CH(CH<sub>3</sub>)CH<sub>3</sub>, -C(CH<sub>3</sub>)<sub>3</sub>, -CH<sub>2</sub>Ph, or

10



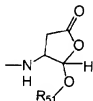
, wherein

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$R_{13}$  is  $-\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $-\text{CH}(\text{CH}_3)(\text{CH}_3)$ ,  
 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $-\text{CH}_2-\text{CH}(\text{CH}_3)\text{CH}_3$ ,  $-\text{C}(\text{CH}_3)_3$ ,  $-\text{CH}_2\text{Ph}$ ,  
 or , and

each  $R_{51}$  is  $-\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_3$ ,  
 5  $-\text{CH}(\text{CH}_3)(\text{CH}_3)$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $-\text{CH}_2-\text{CH}(\text{CH}_3)\text{CH}_3$ ,  $-\text{C}(\text{CH}_3)_3$ ,  
 $-\text{CH}_2\text{Ph}$ , or taken together form a ethylenedioxy acetal  
 or a propylenedioxy acetal; or

10



, wherein

$R_{51}$  is  $-\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $-\text{CH}(\text{CH}_3)(\text{CH}_3)$ ,  
 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $-\text{CH}_2-\text{CH}(\text{CH}_3)\text{CH}_3$ ,  $-\text{C}(\text{CH}_3)_3$ ,  $-\text{CH}_2\text{Ph}$ ,  
 $-\text{C}(\text{O})-\text{CH}_3$  or  $-\text{C}(\text{O})-\text{Ph}$ ;

15  $R_5$  in each of the above compounds is the same as  
 any one of the  $R_5$  moieties shown for any one of  
 compounds 139, 214c, 214e, 404-413, 415-491, 493-501.

Specific compounds of this invention also include,  
 but are not limited to, compounds comprising scaffolds  
 20 1-28, wherein  $R$ ,  $R_{51}$ , and  $R_5$  are as defined above, and  
 in which the  $-\text{C}(\text{O})-$  of the  $R_5$  moiety of any one of  
 compounds 214c, 214e, 404-413, 415-418, 422-426, 430-  
 456, 458-466, 468, 470-471, 473-491, 493, 495, 497-501  
 is replaced with  $-\text{CH}_2-$ ,  $-\text{C}(\text{O})\text{C}(\text{O})-$ , or  $-\text{CH}_2\text{C}(\text{O})\text{C}(\text{O})-$ .

25 The ICE inhibitors of another embodiment (D)  
 of this invention are those of formula (I):

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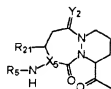
(I)



wherein:

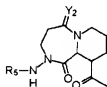
5  $R_1$  is selected from the group consisting of the following formulae:

(e10)



;

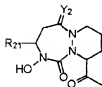
(e11)



;

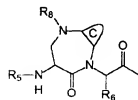
10

(e12)



;

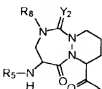
(w2)



;

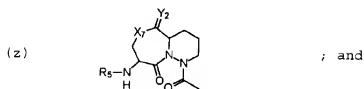
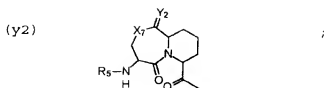
15

(y1)



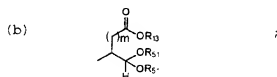
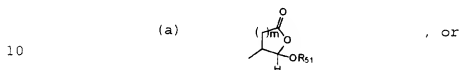
;

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ring C is chosen from the group consisting of  
 5 benzo, pyrido, thieno, pyrrolo, furano, thiazolo,  
 isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo,  
 cyclopentyl, and cyclohexyl;

R<sub>2</sub> is:



m is 1 or 2;

15 each R<sub>5</sub> is independently selected from the group  
 consisting of:

- C(O)-R<sub>10</sub>,
- C(O)O-R<sub>9</sub>,
- C(O)-N(R<sub>10</sub>)(R<sub>10</sub>)
- S(O)<sub>2</sub>-R<sub>9</sub>,

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-S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
 -C(O)-CH<sub>2</sub>-O-R<sub>9</sub>,  
 -C(O)C(O)-R<sub>10</sub>,  
 -R<sub>9</sub>,  
 5        -H,  
          -C(O)C(O)-OR<sub>10</sub>, and  
          -C(O)C(O)-N(R<sub>9</sub>)(R<sub>10</sub>);

X<sub>5</sub> is  $\begin{array}{c} \text{-CH-} \\ | \end{array}$  or  $\begin{array}{c} \text{-N-} \\ | \end{array}$ ;

10        Y<sub>2</sub> is H<sub>2</sub> or O;

X<sub>7</sub> is -N(R<sub>8</sub>)- or -O-;

15        R<sub>6</sub> is selected from the group consisting of -H and  
          -CH<sub>3</sub>;

R<sub>8</sub> is selected from the group consisting of:

20        -C(O)-R<sub>10</sub>,  
          -C(O)O-R<sub>9</sub>,  
          -C(O)-N(H)-R<sub>10</sub>,  
          -S(O)<sub>2</sub>-R<sub>9</sub>,  
          -S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
          -C(O)-CH<sub>2</sub>-OR<sub>10</sub>,  
          -C(O)C(O)-R<sub>10</sub>;  
 25        -C(O)-CH<sub>2</sub>N(R<sub>10</sub>)(R<sub>10</sub>),  
          -C(O)-CH<sub>2</sub>C(O)-O-R<sub>9</sub>,  
          -C(O)-CH<sub>2</sub>C(O)-R<sub>9</sub>,  
          -H, and  
          -C(O)-C(O)-OR<sub>10</sub>;

30        each R<sub>9</sub> is independently selected from the group  
          consisting of -Ar<sub>3</sub> and a -C<sub>1-6</sub> straight or branched  
          alkyl group optionally substituted with Ar<sub>3</sub>, wherein

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the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

each R<sub>10</sub> is independently selected from the group consisting of -H, -Ar<sub>3</sub>, a C<sub>3-6</sub> cycloalkyl group, and a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, wherein the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

R<sub>13</sub> is selected from the group consisting of H, Ar<sub>3</sub>, and a C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, -CONH<sub>2</sub>, -OR<sub>5</sub>, -OH, -OR<sub>9</sub>, or -CO<sub>2</sub>H;

each R<sub>51</sub> is independently selected from the group consisting of R<sub>9</sub>, -C(O)-R<sub>9</sub>, -C(O)-N(H)-R<sub>9</sub>, or each R<sub>51</sub> taken together forms a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-;

each R<sub>21</sub> is independently selected from the group consisting of -H or a -C<sub>1-6</sub> straight or branched alkyl group;

each Ar<sub>3</sub> is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Q<sub>1</sub> is independently selected from the group



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consisting of  $-\text{NH}_2$ ,  $-\text{CO}_2\text{H}$ ,  $-\text{Cl}$ ,  $-\text{F}$ ,  $-\text{Br}$ ,  $-\text{I}$ ,  $-\text{NO}_2$ ,  $-\text{CN}$ ,  
 $=\text{O}$ ,  $-\text{OH}$ ,  $-\text{perfluoro C}_{1-3}$  alkyl,  $\text{R}_5$ ,  $-\text{OR}_5$ ,  $-\text{NHR}_5$ ,  $\text{OR}_5$ ,  
 $-\text{N}(\text{R}_9)(\text{R}_{10})$ ,  $\text{R}_9$ ,  $-\text{C}(\text{O})-\text{R}_{10}$ , and



10 provided that when  $-\text{Ar}_3$  is substituted with a  $\text{Q}_1$  group which comprises one or more additional  $-\text{Ar}_3$  groups, said additional  $-\text{Ar}_3$  groups are not substituted with another  $-\text{Ar}_3$ .

Preferably,  $\text{R}_5$  is selected from the group  
 15 consisting of:  
 $-\text{C}(\text{O})-\text{R}_{10}$ ,  
 $-\text{C}(\text{O})\text{O}-\text{R}_9$ , and  
 $-\text{C}(\text{O})-\text{NH}-\text{R}_{10}$ .

Alternatively,  $\text{R}_5$  is selected from the group  
 20 consisting of:  
 $-\text{S}(\text{O})_2-\text{R}_9$ ,  
 $-\text{S}(\text{O})_2-\text{NH}-\text{R}_{10}$ ,  
 $-\text{C}(\text{O})-\text{C}(\text{O})-\text{R}_{10}$ ,  
 $-\text{R}_9$ , and  
 25  $-\text{C}(\text{O})-\text{C}(\text{O})-\text{OR}_{10}$ .

More preferably:

$m$  is 1;

$\text{R}_{13}$  is H or a  $-\text{C}_{1-4}$  straight or branched alkyl group optionally substituted with  $-\text{Ar}_3$ ,  $-\text{OH}$ ,  $-\text{OR}_9$ , or  
 30  $-\text{CO}_2\text{H}$ , wherein the  $\text{R}_9$  is a  $-\text{C}_{1-4}$  branched or straight alkyl group, wherein  $\text{Ar}_3$  is morpholinyl or phenyl, wherein the phenyl is optionally substituted with  $\text{Q}_1$ ;

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$R_{21}$  is -H or  $-CH_3$ ;

$R_{51}$  is a  $C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$ , wherein  $Ar_3$  is phenyl, optionally substituted by  $-Q_1$ ;

5

each  $Ar_3$  cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinoliny, isoquinoliny, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

10

each  $Q_1$  is independently selected from the group consisting of  $-NH_2$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-OH$ ,  $-R_9$ ,  $-NH-R_5$  wherein  $R_5$  is  $-C(O)-R_{10}$  or  $-S(O)_2-R_9$ ,  $-OR_5$  wherein  $R_5$  is  $-C(O)-R_{10}$ ,  $-OR_9$ ,  $-N(R_9)(R_{10})$ , and

15

20



wherein each  $R_9$  and  $R_{10}$  are independently a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$  wherein  $Ar_3$  is phenyl;

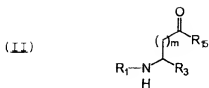
25

provided that when  $-Ar_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-Ar_3$  groups, said additional  $-Ar_3$  groups are not substituted with another  $-Ar_3$ .

30

The ICE inhibitors of another embodiment (E) of this invention are those of formula (II):

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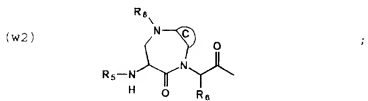
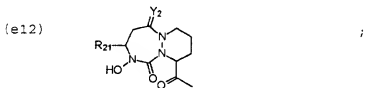
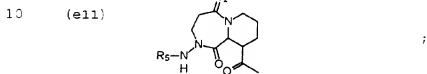
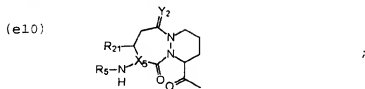


wherein:

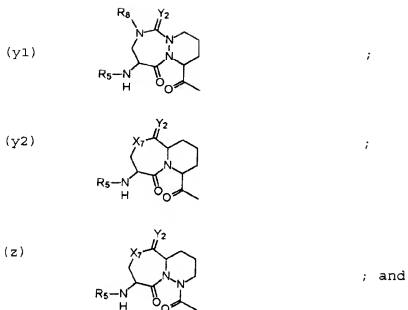
m is 1 or 2;

5

R<sub>1</sub> is selected from the group consisting of the following formulae:



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ring C is chosen from the group consisting of  
benzo, pyrido, thieno, pyrrolo, furano, thiazolo,  
isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo,  
cyclopentyl, and cyclohexyl;

R<sub>3</sub> is selected from the group consisting of:

- CN,
- C(O)-H,
- C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>,
- C(O)-CH<sub>2</sub>-F,
- C=N-O-R<sub>9</sub>, and
- CO-Ar<sub>2</sub>;

each R<sub>5</sub> is independently selected from the group  
consisting of:

- C(O)-R<sub>10</sub>,
- C(O)O-R<sub>9</sub>,
- C(O)-N(R<sub>10</sub>)(R<sub>10</sub>)
- S(O)<sub>2</sub>-R<sub>9</sub>,
- S(O)<sub>2</sub>-NH-R<sub>10</sub>,

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$\text{-C(O)-CH}_2\text{-O-R}_9$ ,  
 $\text{-C(O)C(O)-R}_{10}$ ,  
 $\text{-R}_9$ ,  
 $\text{-H}$ ,  
 5  $\text{-C(O)C(O)-OR}_{10}$ , and  
 $\text{-C(O)C(O)-N(R}_9\text{)(R}_{10}\text{)}$ ;

$\text{X}_5$  is  $\text{-CH-}$  or  $\text{-N-}$ ;  
 $\quad \quad \quad | \quad \quad \quad |$   
 10  $\text{Y}_2$  is  $\text{H}_2$  or  $\text{O}$ ;  
 $\text{X}_7$  is  $\text{-N(R}_8\text{)-}$  or  $\text{-O-}$ ;

each  $\text{T}_1$  is independently selected from the group consisting of  $\text{-O-}$ ,  $\text{-S-}$ ,  $\text{-S(O)-}$ , and  $\text{-S(O)}_2\text{-}$ ;

15  $\text{R}_6$  is selected from the group consisting of  $\text{-H}$  and  $\text{-CH}_3$ ;

$\text{R}_8$  is selected from the group consisting of:  
 $\text{-C(O)-R}_{10}$ ,  
 20  $\text{-C(O)O-R}_9$ ,  
 $\text{-C(O)-NH-R}_{10}$ ,  
 $\text{-S(O)}_2\text{-R}_9$ ,  
 $\text{-S(O)}_2\text{-NH-R}_{10}$ ,  
 $\text{-C(O)-CH}_2\text{-OR}_{10}$ ,  
 25  $\text{-C(O)C(O)-R}_{10}$ ,  
 $\text{-C(O)-CH}_2\text{-N(R}_{10}\text{)(R}_{10}\text{)}$ ,  
 $\text{-C(O)-CH}_2\text{C(O)-O-R}_9$ ,  
 $\text{-C(O)-CH}_2\text{C(O)-R}_9$ ,  
 $\text{-H}$ , and  
 30  $\text{-C(O)-C(O)-OR}_{10}$ ;

each  $\text{R}_9$  is independently selected from the group consisting of  $\text{-Ar}_3$  and a  $\text{-C}_{1-6}$  straight or branched alkyl group optionally substituted with  $\text{Ar}_3$ , wherein

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the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

each R<sub>10</sub> is independently selected from the group consisting of -H, -Ar<sub>3</sub>, a C<sub>3-6</sub> cycloalkyl group, and a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, wherein the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

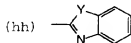
each R<sub>11</sub> is independently selected from the group consisting of:

-Ar<sub>4</sub>,  
- (CH<sub>2</sub>)<sub>1-3</sub>-Ar<sub>4</sub>,  
-H, and  
-C(O)-Ar<sub>4</sub>;

R<sub>15</sub> is selected from the group consisting of -OH, -OAr<sub>3</sub>, -N(H)-OH, and a -OC<sub>1-6</sub> straight or branched alkyl group optionally substituted with -Ar<sub>3</sub>, -CONH<sub>2</sub>, -OR<sub>5</sub>, -OH, -OR<sub>9</sub>, or -CO<sub>2</sub>H;

each R<sub>21</sub> is independently selected from the group consisting of -H or a -C<sub>1-6</sub> straight or branched alkyl group;

Ar<sub>2</sub> is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by -Q<sub>1</sub>:



, and

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(ii)



wherein each Y is independently selected from the group consisting of O and S;

5 each Ar<sub>3</sub> is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said  
10 heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, and -NH-, -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings,  
15 and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Ar<sub>4</sub> is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3  
20 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, -NH-, -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally  
25 containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Q<sub>1</sub> is independently selected from the group  
30 consisting of -NH<sub>2</sub>, -CO<sub>2</sub>H, -Cl, -F, -Br, -I, -NO<sub>2</sub>, -CN, -O, -OH, -perfluoro C<sub>1-3</sub> alkyl, R<sub>5</sub>, -OR<sub>5</sub>, -NHR<sub>5</sub>, OR<sub>9</sub>, -N(R<sub>9</sub>)(R<sub>10</sub>), R<sub>9</sub>, -C(O)-R<sub>10</sub>, and

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5

provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub> group which comprises one or more additional -Ar<sub>3</sub> groups, said additional -Ar<sub>3</sub> groups are not substituted with another -Ar<sub>3</sub>.

10

Preferred compounds of embodiment E employ formula (II), wherein R<sub>1</sub> is (e11) and the other substituents are as defined above.

Other preferred compounds of embodiment E employ formula (II), wherein R<sub>1</sub> is (e12) and the other substituents are as defined above.

15

Other preferred compounds of embodiment E employ formula (II) wherein R<sub>1</sub> is (y1) and the other substituents are as defined above.

Other preferred compounds of embodiment E employ formula (II) wherein R<sub>1</sub> is (y2) and the other substituents are as defined above.

20

Other preferred compounds of embodiment E of employ formula (II) wherein R<sub>1</sub> is (z) and the other substituents are as defined above.

25

Other preferred compound of embodiment E employ formula (II) wherein R<sub>1</sub> is (w2) and the other substituents are as defined above.

More preferably, R<sub>1</sub> is (w2) and



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m is 1;

ring C is benzo, pyrido, or thieno;

R<sub>3</sub> is selected from the group consisting of  
-C(O)-H, -C(O)-Ar<sub>2</sub>, and -C(O)CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>;

- 5 R<sub>5</sub> is selected from the group consisting of:  
-C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is -Ar<sub>3</sub>;  
-C(O)O-R<sub>9</sub>, wherein R<sub>9</sub> is -CH<sub>2</sub>-Ar<sub>3</sub>;  
-C(O)C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is -Ar<sub>3</sub>;  
-R<sub>9</sub>, wherein R<sub>9</sub> is a C<sub>1-2</sub> alkyl group  
10 substituted with -Ar<sub>3</sub>; and  
-C(O)C(O)-OR<sub>10</sub>, wherein R<sub>10</sub> is -CH<sub>2</sub>Ar<sub>3</sub>;

T<sub>1</sub> is O or S;

R<sub>6</sub> is H;

- 15 R<sub>8</sub> is selected from the group consisting -C(O)-R<sub>10</sub>,  
-C(O)-CH<sub>2</sub>-OR<sub>10</sub>, and -C(O)CH<sub>2</sub>-N(R<sub>10</sub>)(R<sub>10</sub>), wherein R<sub>10</sub> is  
H, CH<sub>3</sub>, or -CH<sub>2</sub>CH<sub>3</sub>;

R<sub>11</sub> is selected from the group consisting of -Ar<sub>4</sub>,  
-(CH<sub>2</sub>)<sub>1-3</sub>-Ar<sub>4</sub>, and -C(O)-Ar<sub>4</sub>;

- 20 R<sub>15</sub> is -OH or -OC<sub>1-4</sub> straight or branched alkyl  
group optionally substituted with -Ar<sub>3</sub>, -OH, -OR<sub>9</sub>, or  
-CO<sub>2</sub>H, wherein the R<sub>9</sub> is a -C<sub>1-4</sub> branched or straight  
alkyl group, wherein Ar<sub>3</sub> is morpholinyl or phenyl,  
wherein the phenyl is optionally substituted with Q<sub>1</sub>;

- 25 Ar<sub>2</sub> is (hh);

Y is O;

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each Ar<sub>3</sub> cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, thiazolyl, benzimidazolyl, thienothienyl, thiadiazolyl, benzotriazolyl,  
 5 benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Ar<sub>4</sub> cyclic group is independently selected from the set consisting of phenyl, tetrazolyl,  
 10 naphthyl, pyridinyl, oxazolyl, pyrimidinyl, or indolyl, said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Q<sub>1</sub> is independently selected from the group consisting of -NH<sub>2</sub>, -Cl, -F, -Br, -OH, -R<sub>9</sub>, -NH-R<sub>5</sub>  
 15 wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or -S(O)<sub>2</sub>-R<sub>9</sub>, -OR<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub>, -OR<sub>9</sub>, -N(R<sub>9</sub>)(R<sub>10</sub>), and



wherein each R<sub>9</sub> and R<sub>10</sub> are independently a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub> wherein Ar<sub>3</sub> is phenyl;

25 provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub> group which comprises one or more additional -Ar<sub>3</sub> groups, said additional -Ar<sub>3</sub> groups are not substituted with another -Ar<sub>3</sub>.

30 Other preferred compounds of embodiment E employ formula (II) wherein R<sub>1</sub> is (e10), X<sub>5</sub> is CH, and the other substituents are as defined above.

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More preferred compounds of embodiment E employ formula (II) wherein  $R_1$  is (e10),  $X_5$  is CH,  $R_3$  is CO-Ar<sub>2</sub>, and the other substituents are as defined above.

5 Other more preferred compounds of embodiment E employ formula (II) wherein  $R_1$  is (e10),  $X_5$  is CH,  $R_3$  is -C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>,  $R_{11}$  is -(CH<sub>2</sub>)<sub>1-3</sub>-Ar<sub>4</sub>, and the other substituents are as defined above.

10 Other more preferred compounds of embodiment E employ formula (II) wherein  $R_1$  is (e10) and  $X_5$  is CH and  $R_3$  is -C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>, T<sub>1</sub> is O,  $R_{11}$  is -C(O)-Ar<sub>4</sub>, and the other substituents are as defined above.

More preferably, in these more preferred compounds,  $R_5$  is selected from the group consisting of:

15 -C(O)-R<sub>10</sub>,  
-C(O)O-R<sub>9</sub>, and  
-C(O)-NH-R<sub>10</sub>.

Alternatively, in these more preferred compounds,  $R_5$  is selected from the group consisting of:

20 -S(O)<sub>2</sub>-R<sub>9</sub>,  
-S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
-C(O)-C(O)-R<sub>10</sub>,  
-R<sub>9</sub>, and  
-C(O)-C(O)-OR<sub>10</sub>.

25 Most preferably, in these more preferred compounds,

m is 1;

T<sub>1</sub> is O or S;

R<sub>15</sub> is -OH or -OC<sub>1-4</sub> straight or branched alkyl

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group optionally substituted with  $-Ar_3$ ,  $-OH$ ,  $-OR_9$ , or  $-CO_2H$ , wherein the  $R_9$  is a  $-C_{1-4}$  branched or straight alkyl group, wherein  $Ar_3$  is morpholinyl or phenyl, wherein the phenyl is optionally substituted with  $Q_1$ ;

5  $R_{21}$  is  $-H$  or  $-CH_3$ ;

$Ar_2$  is (hh);

$Y$  is  $O$ , and

each  $Ar_3$  cyclic group is independently selected  
 10 from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl,  
 15 and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

each  $Ar_4$  cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl,  
 20 said cyclic group being singly or multiply substituted by  $-Q_1$ ;

each  $Q_1$  is independently selected from the group consisting of  $-NH_2$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-OH$ ,  $-R_9$ ,  $-NH-R_5$  wherein  $R_5$  is  $-C(O)-R_{10}$  or  $-S(O)_2-R_9$ ,  $-OR_5$  wherein  $R_5$  is  
 25  $-C(O)-R_{10}$ ,  $-OR_9$ ,  $-N(R_9)(R_{10})$ , and



wherein each  $R_9$  and  $R_{10}$  are independently a  $-C_{1-6}$

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straight or branched alkyl group optionally substituted with  $\text{Ar}_3$  wherein  $\text{Ar}_3$  is phenyl;

5 provided that when  $-\text{Ar}_3$  is substituted with a  $\text{Q}_1$  group which comprises one or more additional  $-\text{Ar}_3$  groups, said additional  $-\text{Ar}_3$  groups are not substituted with another  $-\text{Ar}_3$ .

Other more preferred compounds of embodiment E employ formula (II) wherein  $\text{R}_1$  is (e10),  $\text{X}_5$  is CH,  $\text{R}_3$  10 is  $-\text{C}(\text{O})-\text{H}$ , and the other substituents are as defined above.

More preferably, in these more preferred compounds,  $\text{R}_5$  is selected from the group consisting of:

15  $-\text{C}(\text{O})-\text{R}_{10}$ ,  
 $-\text{C}(\text{O})\text{O}-\text{R}_9$ , and  
 $-\text{C}(\text{O})-\text{NH}-\text{R}_{10}$ .

Alternatively, in these more preferred compounds,  $\text{R}_5$  is selected from the group consisting of:

20  $-\text{S}(\text{O})_2-\text{R}_9$ ,  
 $-\text{S}(\text{O})_2-\text{NH}-\text{R}_{10}$ ,  
 $-\text{C}(\text{O})-\text{C}(\text{O})-\text{R}_{10}$ ,  
 $-\text{R}_9$ , and  
 $-\text{C}(\text{O})-\text{C}(\text{O})-\text{OR}_{10}$ .

Most preferably, in these more preferred compounds,

25 m is 1;

$\text{R}_{15}$  is  $-\text{OH}$  or  $-\text{OC}_{1-4}$  straight or branched alkyl group optionally substituted with  $-\text{Ar}_3$ ,  $-\text{OH}$ ,  $-\text{OR}_9$ , or  $-\text{CO}_2\text{H}$ , wherein the  $\text{R}_9$  is a  $-\text{C}_{1-4}$  branched or straight alkyl group, wherein  $\text{Ar}_3$  is morpholinyl or phenyl, 30 wherein the phenyl is optionally substituted with  $\text{Q}_1$ ;

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$R_{21}$  is -H or -CH<sub>3</sub>;

each Ar<sub>3</sub> cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Q<sub>1</sub> is independently selected from the group consisting of -NH<sub>2</sub>, -Cl, -F, -Br, -OH, -R<sub>9</sub>, -NH-R<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or -S(O)<sub>2</sub>-R<sub>9</sub>, -OR<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub>, -OR<sub>9</sub>, -N(R<sub>9</sub>)(R<sub>10</sub>), and



wherein each R<sub>9</sub> and R<sub>10</sub> are independently a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub> wherein Ar<sub>3</sub> is phenyl;

provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub> group which comprises one or more additional -Ar<sub>3</sub> groups, said additional -Ar<sub>3</sub> groups are not substituted with another -Ar<sub>3</sub>,

Other more preferred compounds of embodiment E employ formula (II) wherein R<sub>1</sub> is (e10) and X<sub>5</sub> is CH, R<sub>3</sub> is -CO-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>, and R<sub>11</sub> is -Ar<sub>4</sub>, and the other substituents are as defined above.

More preferably, in these more preferred compounds, R<sub>5</sub> is selected from the group consisting of:

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-C(O)-R<sub>10</sub>,  
-C(O)O-R<sub>9</sub>, and  
-C(O)-NH-R<sub>10</sub>.

Alternatively, in these more preferred compounds, R<sub>5</sub> is  
5 selected from the group consisting of:

-S(O)<sub>2</sub>-R<sub>9</sub>,  
-S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
-C(O)-C(O)-R<sub>10</sub>,  
-R<sub>9</sub>, and  
10 -C(O)-C(O)-OR<sub>10</sub>.

Most preferably, in these more preferred compounds,

m is 1;

T<sub>1</sub> is O or S;

15 R<sub>15</sub> is -OH or a -OC<sub>1-4</sub> straight or branched alkyl  
group optionally substituted with -Ar<sub>3</sub>, -OH, -OR<sub>9</sub>, or  
-CO<sub>2</sub>H, wherein the R<sub>9</sub> is a -C<sub>1-4</sub> branched or straight  
alkyl group, wherein Ar<sub>3</sub> is morpholinyl or phenyl,  
wherein the phenyl is optionally substituted with Q<sub>1</sub>;

20 R<sub>21</sub> is -H or -CH<sub>3</sub>;

each Ar<sub>3</sub> cyclic group is phenyl, naphthyl,  
thienyl, quinolinyl, isoquinolinyl, pyrazolyl,  
thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl,  
25 thienothienyl, imidazolyl, thiadiazolyl,  
benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl,  
and said cyclic group optionally being singly or  
multiply substituted by -Q<sub>1</sub>;

each Ar<sub>4</sub> cyclic group is independently selected

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from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl, said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

- 5 each  $Q_1$  is independently selected from the group consisting of  $-\text{NH}_2$ ,  $-\text{Cl}$ ,  $-\text{F}$ ,  $-\text{Br}$ ,  $-\text{OH}$ ,  $-\text{R}_9$ ,  $-\text{NH}-\text{R}_5$  wherein  $\text{R}_5$  is  $-\text{C}(\text{O})-\text{R}_{10}$  or  $-\text{S}(\text{O})_2-\text{R}_9$ ,  $-\text{OR}_5$  wherein  $\text{R}_5$  is  $-\text{C}(\text{O})-\text{R}_{10}$ ,  $-\text{OR}_9$ ,  $-\text{N}(\text{R}_9)(\text{R}_{10})$ , and



- 15 wherein each  $\text{R}_9$  and  $\text{R}_{10}$  are independently a  $\text{C}_{1-6}$  straight or branched alkyl group optionally substituted with  $\text{Ar}_3$  wherein  $\text{Ar}_3$  is phenyl;

- 20 provided that when  $-\text{Ar}_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-\text{Ar}_3$  groups, said additional  $-\text{Ar}_3$  groups are not substituted with another  $-\text{Ar}_3$ .

Other preferred compounds of embodiment E employ formula (II) wherein  $\text{R}_1$  is (e10),  $\text{X}_5$  is N, and the other substituents are as defined above.

- 25 More preferred compounds of embodiment E, employ formula (II) wherein  $\text{R}_1$  is (e10),  $\text{X}_5$  is N,  $\text{R}_3$  is  $\text{CO}-\text{Ar}_2$ , and the other substituents are as defined above.

- 30 Other more preferred compounds of embodiment E, employ formula (II) wherein  $\text{R}_1$  is (e10),  $\text{X}_5$  is N,  $\text{R}_3$  is  $-\text{C}(\text{O})-\text{CH}_2-\text{T}_1-\text{R}_{11}$ ,  $\text{R}_{11}$  is  $-(\text{CH}_2)_{1-3}-\text{Ar}_4$ , and the other substituents are as defined above.



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Other more preferred compounds of embodiment E, employ formula (II) wherein  $R_1$  is (e10) and  $X_5$  is N and:

- 5             $R_3$  is  $-C(O)-CH_2-T_1-R_{11}$ ;  
              $T_1$  is O; and  
              $R_{11}$  is  $-C(O)-Ar_4$ , and the other substituents are as defined above.

- More preferably, in these more preferred compounds,  $R_5$  is selected from the group consisting of:

$-C(O)-R_{10}$ ,  
 $-C(O)O-R_9$ , and  
 $-C(O)-NH-R_{10}$ .

- Alternatively, in these more preferred compounds,  $R_5$  is selected from the group consisting of:

- 15             $-S(O)_2-R_9$ ,  
              $-S(O)_2-NH-R_{10}$ ,  
              $-C(O)-C(O)-R_{10}$ ,  
              $-R_9$ , and  
20             $-C(O)-C(O)-OR_{10}$ .

Most preferably, in these more preferred compounds,  $m$  is 1;

$T_1$  is O or S;

- 25             $R_{15}$  is  $-OH$  or a  $-OC_{1-4}$  straight or branched alkyl group optionally substituted with  $-Ar_3$ ,  $-OH$ ,  $-OR_9$ , or  $-CO_2H$ , wherein the  $R_9$  is a  $-C_{1-4}$  branched or straight alkyl group, wherein  $Ar_3$  is morpholinyl or phenyl, wherein the phenyl is optionally substituted with  $Q_1$ ;

- 30             $R_{21}$  is  $-H$  or  $-CH_3$ ;

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Ar<sub>2</sub> is (hh);

Y is O, and

each Ar<sub>3</sub> cyclic group is independently selected  
 5 from the set consisting of phenyl, naphthyl, thienyl,  
 quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl,  
 isoxazolyl, benzotriazolyl, benzimidazolyl,  
 thienothienyl, imidazolyl, thiadiazolyl,  
 benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl,  
 10 and said cyclic group optionally being singly or  
 multiply substituted by -Q<sub>1</sub>;

each Ar<sub>4</sub> cyclic group is independently selected  
 from the set consisting of phenyl, tetrazolyl,  
 pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl,  
 15 optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Q<sub>1</sub> is independently selected from the group  
 consisting of -NH<sub>2</sub>, -Cl, -F, -Br, -OH, -R<sub>9</sub>, -NH-R<sub>5</sub>  
 wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or -S(O)<sub>2</sub>-R<sub>9</sub>, -OR<sub>5</sub> wherein R<sub>5</sub> is  
 -C(O)-R<sub>10</sub>, -OR<sub>9</sub>, -N(R<sub>9</sub>)(R<sub>10</sub>), and



25 wherein each R<sub>9</sub> and R<sub>10</sub> are independently a -C<sub>1-6</sub>  
 straight or branched alkyl group optionally substituted  
 with Ar<sub>3</sub> wherein Ar<sub>3</sub> is phenyl;

provided that when -Ar<sub>3</sub> is substituted with a Q<sub>2</sub>  
 30 group which comprises one or more additional -Ar<sub>3</sub>  
 groups, said additional -Ar<sub>3</sub> groups are not substituted  
 with another -Ar<sub>3</sub>.

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Other more preferred compounds of embodiment E, employ formula (II) wherein  $R_1$  is (e10),  $X_5$  is N,  $R_3$  is -C(O)-H, and the other substituents are as defined above.

- 5 More preferably, in these more preferred compounds,  $R_5$  is selected from the group consisting of:
- C(O)- $R_{10}$ ,
  - C(O)O- $R_9$ , and
  - C(O)-NH- $R_{10}$ .
- 10 Alternatively, in these more preferred compounds,  $R_5$  is selected from the group consisting of:
- S(O)<sub>2</sub>- $R_9$ ,
  - S(O)<sub>2</sub>-NH- $R_{10}$ ,
  - C(O)-C(O)- $R_{10}$ ,
  - 15 - $R_9$ , and
  - C(O)-C(O)-OR<sub>10</sub>.

Most preferably, in these more preferred compounds,

$m$  is 1;

- 20  $R_{15}$  is -OH or -OC<sub>1-4</sub> straight or branched alkyl group optionally substituted with -Ar<sub>3</sub>, -OH, -OR<sub>9</sub>, or -CO<sub>2</sub>H, wherein the  $R_9$  is a -C<sub>1-4</sub> branched or straight alkyl group, wherein Ar<sub>3</sub> is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q<sub>1</sub>;

- 25  $R_{-1}$  is -H or -CH<sub>3</sub>;

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each Ar<sub>3</sub> cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Q<sub>1</sub> is independently selected from the group consisting of -NH<sub>2</sub>, -Cl, -F, -Br, -OH, -R<sub>9</sub>, -NH-R<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or -S(O)<sub>2</sub>-R<sub>9</sub>, -OR<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub>, -OR<sub>9</sub>, -N(R<sub>9</sub>)(R<sub>10</sub>), and



wherein each R<sub>9</sub> and R<sub>10</sub> are independently a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub> wherein Ar<sub>3</sub> is phenyl;

provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub> group which comprises one or more additional -Ar<sub>3</sub> groups, said additional -Ar<sub>3</sub> groups are not substituted with another -Ar<sub>3</sub>.

Other more preferred compounds of embodiment E, employ formula (II) wherein R<sub>1</sub> is (e10), X<sub>5</sub> is N, R<sub>3</sub> is -CO-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>, R<sub>11</sub> is -Ar<sub>4</sub>, and the other substituents are as defined above.

More preferably, in these more preferred compounds, R<sub>5</sub> is selected from the group consisting of:

-C(O)-R<sub>10</sub>,  
-C(O)O-R<sub>9</sub>, and

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-C(O)-NH-R<sub>10</sub>.

Alternatively, in these more preferred compounds, R<sub>5</sub> is selected from the group consisting of:

- 5           -S(O)<sub>2</sub>-R<sub>9</sub>,  
          -S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
          -C(O)-C(O)-R<sub>10</sub>,  
          -R<sub>9</sub>, and  
          -C(O)-C(O)-OR<sub>10</sub>.

Most preferably, in these more preferred compounds

10           m is 1;

          T<sub>1</sub> is O or S;

          R<sub>15</sub> is -OH or -OC<sub>1-4</sub> straight or branched alkyl  
          group optionally substituted with -Ar<sub>3</sub>, -OH, -OR<sub>9</sub>, or  
15       -CO<sub>2</sub>H, wherein the R<sub>9</sub> is a -C<sub>1-4</sub> branched or straight  
          alkyl group, wherein Ar<sub>3</sub> is morpholinyl or phenyl,  
          wherein the phenyl is optionally substituted with Q<sub>1</sub>;

          R<sub>21</sub> is -H or -CH<sub>3</sub>;

20           each Ar<sub>3</sub> cyclic group is independently selected  
          from the set consisting of phenyl, naphthyl, thienyl,  
          quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl,  
          isoxazolyl, benzotriazolyl, benzimidazolyl,  
          thienothienyl, imidazolyl, thiadiazolyl,  
25       benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl,  
          and said cyclic group optionally being singly or  
          multiply substituted by -Q<sub>1</sub>;

          each Ar<sub>4</sub> cyclic group is independently selected  
          from the set consisting of phenyl, tetrazolyl,  
30       pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl,

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said cyclic group being singly or multiply substituted by  $-Q_1$ ;

each  $Q_1$  is independently selected from the group consisting of  $-\text{NH}_2$ ,  $-\text{Cl}$ ,  $-\text{F}$ ,  $-\text{Br}$ ,  $-\text{OH}$ ,  $-\text{R}_9$ ,  $-\text{NH}-\text{R}_5$  wherein  $\text{R}_5$  is  $-\text{C}(\text{O})-\text{R}_{10}$  or  $-\text{S}(\text{O})_2-\text{R}_9$ ,  $-\text{OR}_5$  wherein  $\text{R}_5$  is  $-\text{C}(\text{O})-\text{R}_{10}$ ,  $-\text{OR}_9$ ,  $-\text{N}(\text{R}_9)(\text{R}_{10})$ , and



wherein each  $\text{R}_9$  and  $\text{R}_{10}$  are independently a  $-\text{C}_{1-6}$  straight or branched alkyl group optionally substituted with  $\text{Ar}_3$  wherein  $\text{Ar}_3$  is phenyl;

15 provided that when  $-\text{Ar}_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-\text{Ar}_3$  groups, said additional  $-\text{Ar}_3$  groups are not substituted with another  $-\text{Ar}_3$ .

20 The ICE inhibitors of another embodiment (F) of this invention are those of formula (III):

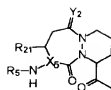


25 wherein:

$\text{R}_1$  is selected from the group consisting of the following formulae:

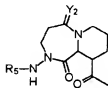
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(e10)



;

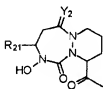
(e11)



;

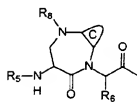
5

(e12)



;

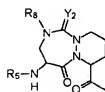
(w2)



;

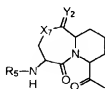
10

(y1)



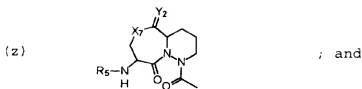
;

(y2)



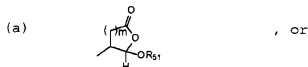
;

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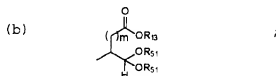


ring C is chosen from the group consisting of  
benzo, pyrido, thieno, pyrrolo, furano, thiazolo,  
isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo,  
cyclopentyl, and cyclohexyl;

R<sub>2</sub> is:



10



m is 1 or 2;

each R<sub>5</sub> is independently selected from  
the group consisting of:

15

- C(O)-R<sub>10</sub>,
- C(O)O-R<sub>9</sub>,
- C(O)-N(R<sub>10</sub>)(R<sub>10</sub>)
- S(O)<sub>2</sub>-R<sub>9</sub>,
- S(O)<sub>2</sub>-NH-R<sub>10</sub>,
- C(O)-CH<sub>2</sub>-O-R<sub>9</sub>,
- C(O)C(O)-R<sub>10</sub>,
- R<sub>9</sub>,
- H,

20



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-C(O)C(O)-OR<sub>10</sub>, and  
-C(O)C(O)-N(R<sub>3</sub>)(R<sub>10</sub>);

X<sub>5</sub> is CH or N;

5 Y<sub>2</sub> is H<sub>2</sub> or O;

X<sub>7</sub> is -N(R<sub>8</sub>)- or -O-;

10 R<sub>6</sub> is selected from the group consisting of -H and  
-CH<sub>3</sub>;

R<sub>8</sub> is selected from the group consisting of:

-C(O)-R<sub>10</sub>,  
-C(O)O-R<sub>9</sub>,  
15 -C(O)-N(H)-R<sub>10</sub>,  
-S(O)<sub>2</sub>-R<sub>9</sub>,  
-S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
-C(O)-CH<sub>2</sub>-OR<sub>10</sub>,  
-C(O)C(O)-R<sub>10</sub>;  
20 -C(O)-CH<sub>2</sub>N(R<sub>10</sub>)(R<sub>10</sub>),  
-C(O)-CH<sub>2</sub>C(O)-O-R<sub>9</sub>,  
-C(O)-CH<sub>2</sub>C(O)-R<sub>9</sub>,  
-H, and  
-C(O)-C(O)-OR<sub>10</sub>;

25 each R<sub>9</sub> is independently selected from the group  
consisting of -Ar<sub>3</sub> and a -C<sub>1-6</sub> straight or branched  
alkyl group optionally substituted with Ar<sub>3</sub>, wherein  
the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

30 each R<sub>10</sub> is independently selected from the group  
consisting of -H, -Ar<sub>3</sub>, a C<sub>3-6</sub> cycloalkyl group, and a  
-C<sub>1-6</sub> straight or branched alkyl group optionally  
substituted with Ar<sub>3</sub>, wherein the -C<sub>1-6</sub> alkyl group is

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optionally unsaturated;

$R_{13}$  is selected from the group consisting of H,  $Ar_3$ , and a  $C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$ ,  $-CONH_2$ ,  $-OR_5$ ,  $-OH$ ,  
 5  $-OR_9$ , or  $-CO_2H$ ;

each  $R_{21}$  is independently selected from the group consisting of  $-H$  or a  $-C_{1-6}$  straight or branched alkyl group;

each  $R_{51}$  is independently selected from the group  
 10 consisting of  $R_9$ ,  $-C(O)-R_9$ ,  $-C(O)-N(H)-R_9$ , or each  $R_{51}$  taken together forms a saturated 4-8 member carbocyclic ring or heterocyclic ring containing  $-O-$ ,  $-S-$ , or  $-NH-$ ;

each  $Ar_3$  is a cyclic group independently selected from the set consisting of an aryl group which contains  
 15 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from  $-O-$ ,  $-S-$ ,  $-SO-$ ,  $SO_2$ ,  $=N-$ , and  $-NH-$ ,  
 20 said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

25 each  $Q_1$  is independently selected from the group consisting of  $-NH_2$ ,  $-CO_2H$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-I$ ,  $-NO_2$ ,  $-CN$ ,  $=O$ ,  $-OH$ ,  $-perfluoro\ C_{1-3}\ alkyl$ ,  $R_5$ ,  $-OR_5$ ,  $-NHR_5$ ,  $OR_9$ ,  $-N(R_9)(R_{10})$ ,  $R_9$ ,  $-C(O)-R_{10}$ , and

30



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provided that when  $-\text{Ar}_3$  is substituted with a  $\text{Q}_1$  group which comprises one or more additional  $-\text{Ar}_3$  groups, said additional  $-\text{Ar}_3$  groups are not substituted with another  $-\text{Ar}_3$ .

Preferred compounds of embodiment F employ formula (III), wherein  $\text{R}_1$  is (w2) and the other substituents are as defined above.

Preferably, when  $\text{R}_1$  is (w2):

m is 1;

ring C is benzo, pyrido, or thieno;

$\text{R}_5$  is selected from the group consisting of:

- C(O)- $\text{R}_{10}$ , wherein  $\text{R}_{10}$  is  $-\text{Ar}_3$ ;
- C(O)O- $\text{R}_9$ , wherein  $\text{R}_9$  is  $-\text{CH}_2-\text{Ar}_3$ ;
- C(O)C(O)- $\text{R}_{10}$ , wherein  $\text{R}_{10}$  is  $-\text{Ar}_3$ ;
- $\text{R}_9$ , wherein  $\text{R}_9$  is a  $\text{C}_{1-2}$  alkyl group substituted with  $-\text{Ar}_3$ ; and
- C(O)C(O)- $\text{OR}_{10}$ , wherein  $\text{R}_{10}$  is  $-\text{CH}_2\text{Ar}_3$ ;

$\text{R}_6$  is H;

$\text{R}_3$  is selected from the group consisting  $-\text{C(O)}-\text{R}_{10}$ ,  $-\text{C(O)}-\text{CH}_2-\text{OR}_{10}$ , and  $-\text{C(O)}\text{CH}_2-\text{N}(\text{R}_{10}) (\text{R}_{10})$ , wherein  $\text{R}_{10}$  is H,  $\text{CH}_3$ , or  $-\text{CH}_2\text{CH}_3$ ;

$\text{R}_{13}$  is H or a  $\text{C}_{1-4}$  straight or branched alkyl group optionally substituted with  $\text{Ar}_3$ ,  $-\text{OH}$ ,  $-\text{OR}_9$ ,  $-\text{CO}_2\text{H}$ , wherein the  $\text{R}_9$  is a  $\text{C}_{1-4}$  branched or straight chain alkyl group; wherein  $\text{Ar}_3$  is morpholinyl or phenyl, wherein the phenyl is optionally substituted with  $\text{Q}_1$ ;

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Ar<sub>3</sub> is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, thiazolyl, benzimidazolyl, thienothienyl, thiadiazolyl, benzotriazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl;

each Q<sub>1</sub> is independently selected from the group consisting of -NH<sub>2</sub>, -Cl, -F, -Br, -OH, -R<sub>9</sub>, -NH-R<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or -S(O)<sub>2</sub>-R<sub>9</sub>, -OR<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub>, -OR<sub>9</sub>, -NHR<sub>9</sub>, and

10



wherein each R<sub>9</sub> and R<sub>10</sub> are independently a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub> wherein Ar<sub>3</sub> is phenyl;

provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub> group which comprises one or more additional -Ar<sub>3</sub> groups, said additional -Ar<sub>3</sub> groups are not substituted with another -Ar<sub>3</sub>.

Other preferred compounds of embodiment F employ formula (III), wherein R<sub>1</sub> is (e11) and the other substituents are as defined above.

Other preferred compounds of embodiment F employ formula (III), wherein R<sub>1</sub> is (e12) and the other substituents are as defined above.

Other preferred compounds of embodiment F employ formula (III), wherein R<sub>1</sub> is (y1) and the other substituents are as defined above.

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Other preferred compounds of embodiment F employ formula (III), wherein  $R_1$  is (y2) and the other substituents are as defined above.

5 Other preferred compounds of embodiment F employ formula (III), wherein  $R_1$  is (z) and the other substituents are as defined above.

Other preferred compounds of embodiment F employ formula (III), wherein  $R_1$  is (e10) and  $X_5$  is CH (also referred to herein as e10-B), and the other  
10 substituents are as defined above.

Other preferred compounds of embodiment F employ formula (III), wherein  $R_1$  is (e10) and  $X_5$  is N, (also referred to herein as e10-A) and the other substituents are as defined above.

15 Preferably, when  $R_1$  is (e11), (e12), (y1), (y2), (z), (e10-A), and (e10-B),  $R_5$  is selected from the group consisting of:

-C(O)- $R_{10}$ ,  
-C(O)O- $R_9$ , and  
20 -C(O)-NH- $R_{10}$ .

Alternatively, when  $R_1$  is (e11), (e12), (y1), (y2), (z), (e10-A), and (e10-B),  $R_5$  is selected from the group consisting of:

-S(O)<sub>2</sub>- $R_9$ ,  
25 -S(O)<sub>2</sub>-NH- $R_{10}$ ,  
-C(O)-C(O)- $R_{10}$ ,  
- $R_9$ ,  
-C(O)-C(O)-OR<sub>10</sub>, and  
-C(O)C(O)-N( $R_9$ )( $R_{10}$ ).

30 More preferably,  $R_5$  is R-C(O)-C(O)- $R_{10}$ .

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Alternatively,  $R_5$  is  $-C(O)-C(O)-OR_{10}$ .

More preferably when  $R_1$  is (e11), (e12), (y1), (y2), (z), (e10-A), and (e10-B):

m is 1;

5  $R_{21}$  is -H or  $-CH_3$ ;

$R_{51}$  is a  $C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$ , wherein the  $Ar_3$  cyclic group is phenyl, said cyclic group optionally being multiply or singly substituted by  $-Q_1$ ;

10 each  $Ar_3$  cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl,  
15 benzo[b]thiophenyl, pyridyl, benzofuranyl, or indolyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

each  $Q_1$  is independently selected from the group consisting of  $-NH_2$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-OH$ ,  $-R_9$ ,  $-NH-R_5$ ,  
20 wherein  $R_5$  is  $-C(O)-R_{10}$  or  $-S(O)_2-R_9$ ,  $-OR_5$  wherein  $R_5$  is  $-C(O)-R_{10}$ ,  $-OR_9$ ,  $-N(R_9)(R_{10})$ , and

25 
$$\begin{array}{c} O \\ / \quad \backslash \\ CH_2, \\ \backslash \quad / \\ O \end{array}$$

wherein each  $R_9$  and  $R_{10}$  are independently a  $-C_{1-6}$  straight or branched alkyl group optionally substituted  
30 with  $Ar_3$ , wherein the  $Ar_3$  cyclic group is phenyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

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provided that when  $-Ar_3$  is substituted with a  $-Q_1$  group which comprises one or more additional  $-Ar_3$  groups, said additional  $-Ar_3$  groups are not substituted with another  $-Ar_3$ .

More preferably, in these more preferred compounds, the  $Ar_3$  cyclic group is selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ .

Compounds in a preferred form of this embodiment F are those wherein:

$R_5$  is  $-C(O)-R_{10}$ , wherein:

$R_{10}$  is  $Ar_3$ , wherein the  $Ar_3$  cyclic group is phenyl, said cyclic group optionally being singly or multiply substituted by:

$-F$ ,  
 $-Cl$ ,  
 $-N(H)-R_5$ , wherein  $-R_5$  is  $-H$  or  $-C(O)-R_{10}$ , wherein  $R_{10}$  is a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$ , wherein the  $Ar_3$  cyclic group is phenyl, said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ,  
 $-N(R_9)(R_{10})$ , wherein  $R_9$  and  $R_{10}$  are independently a  $-C_{1-4}$  straight or branched alkyl group, or  
 $-O-R_5$ , wherein  $R_5$  is  $H$  or a  $-C_{1-4}$  straight or branched alkyl group.

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More preferably the Ar<sub>3</sub> cyclic group is phenyl optionally being singly or multiply substituted at the 3- or 5-position by -Cl or at the 4-position by -NH-R<sub>5</sub>, -N(R<sub>9</sub>)(R<sub>10</sub>), or -O-R<sub>5</sub>.

5 Other preferred compounds of embodiment F include those wherein R<sub>5</sub> is -C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is Ar<sub>3</sub> and the Ar<sub>3</sub> cyclic group is selected from the group consisting of indolyl, benzimidazolyl, thienyl, and benzo[b]thiophenyl, and said cyclic group optionally  
10 being singly or multiply substituted by -Q<sub>1</sub>;

Other preferred compounds of embodiment F include those wherein R<sub>5</sub> is -C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is Ar<sub>3</sub> and the Ar<sub>3</sub> cyclic group is selected from quinolyl and isoquinolyl, and said cyclic group optionally being  
15 singly or multiply substituted by -Q<sub>1</sub>.

Other preferred compounds of embodiment F are those wherein R<sub>5</sub> is -C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is Ar<sub>3</sub>, wherein the Ar<sub>3</sub> cyclic group is phenyl, substituted by



25 In another form of embodiment F the compounds are as described above, further provided that when:

m is 1;  
R<sub>1</sub> is (e10);  
X<sub>5</sub> is CH;  
R<sub>15</sub> is -OH;  
30 R<sub>21</sub> is -H; and



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$Y_2$  is O and  $R_3$  is  $-C(O)-H$ , then  $R_5$  cannot be:

$-C(O)-R_{10}$ , wherein  $R_{10}$  is  $-Ar_3$  and the  $Ar_3$  cyclic group is phenyl, unsubstituted by  $-Q_1$ , 4-(carboxymethoxy)phenyl, 2-fluorophenyl, 2-pyridyl, N-(4-methylpiperazino)methylphenyl, or

$-C(O)-OR_9$ , wherein  $R_9$  is  $-CH_2-Ar_3$ , and the  $Ar_3$  cyclic group is phenyl, unsubstituted by  $-Q_1$ ; and when

$Y_2$  is O,  $R_3$  is  $-C(O)-CH_2-T_1-R_{11}$ ,  $T_1$  is O, and  $R_{11}$  is  $Ar_4$ , wherein the  $Ar_4$  cyclic group is 5-(1-(4-chlorophenyl)-3-trifluoromethyl)pyrazolyl), then  $R_5$  cannot be:

$-C(O)-R_{10}$ , wherein  $R_{10}$  is  $-Ar_3$  and the  $Ar_3$  cyclic group is 4-(dimethylaminomethyl)phenyl, phenyl, 4-(carboxymethylthio)phenyl, 4-(carboxyethylthio)phenyl, 4-(carboxyethyl)phenyl, 4-(carboxypropyl)phenyl, 2-fluorophenyl, 2-pyridyl, N-(4-methylpiperazino)methylphenyl, or

$-C(O)-OR_9$ , wherein  $R_9$  is  $-CH_2-Ar_3$  and the  $Ar_3$  cyclic group is phenyl;

and when  $R_{11}$  is  $Ar_4$ , wherein the  $Ar_4$  cyclic group is 5-(1-phenyl-3-trifluoromethyl)pyrazolyl), then  $R_5$  cannot be:

$-C(O)-OR_9$ , wherein  $R_9$  is  $-CH_2-Ar_3$ , and the  $Ar_3$  cyclic group is phenyl;

and when  $R_{11}$  is  $Ar_4$ , wherein the  $Ar_4$  cyclic group is 5-(1-(2-pyridyl)-3-trifluoromethyl)pyrazolyl), then  $R_5$  cannot be:

$-C(O)-R_{10}$ , wherein  $R_{10}$  is  $-Ar_3$  and the  $Ar_3$  cyclic group is 4-(dimethylaminomethyl)phenyl, or

$-C(O)-OR_9$ , wherein  $R_9$  is  $-CH_2-Ar_3$ , and the  $Ar_3$  cyclic group is phenyl, unsubstituted by  $-Q_1$ ; and when

$Y_2$  is O,  $R_3$  is  $-C(O)-CH_2-T_1-R_{11}$ ,  $T_1$  is O, and  $R_{11}$  is  $-C(O)-Ar_4$ , wherein the  $Ar_4$  cyclic group is 2,5-

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dichlorophenyl, then  $R_5$  cannot be:

-C(O)- $R_{10}$ , wherein  $R_{10}$  is - $Ar_3$  and the  $Ar_3$  cyclic group is 4-(dimethylaminomethyl)phenyl, 4-(N-morpholinomethyl)phenyl, 4-(N-methylpiperazino)methyl)phenyl, 4-(N-(2-methylimidazolylmethyl)phenyl, 5-benzimidazolyl, 5-benzotriazolyl, N-carboethoxy-5-benzotriazolyl, N-carboethoxy-5-benzimidazolyl, or

10 -C(O)- $OR_9$ , wherein  $R_9$  is - $CH_2-Ar_3$ , and the  $Ar_3$  cyclic group is phenyl, unsubstituted by - $Q_1$ ; and when

$Y_2$  is  $H_2$ ,  $R_3$  is -C(O)- $CH_2-T_1-R_{11}$ ,  $T_1$  is O, and  $R_{11}$  is

-C(O)- $Ar_4$ , wherein the  $Ar_4$  cyclic group is 2,5-dichlorophenyl, then  $R_5$  cannot be:

15 -C(O)- $OR_9$ , wherein  $R_9$  is - $CH_2-Ar_3$  and the  $Ar_3$  cyclic group is phenyl.

In another form of embodiment F, preferred compounds are those wherein  $R_{21}$  is -H.

20 Alternatively, preferred compounds are those wherein  $R_{21}$  is - $CH_3$ .

Preferred compounds of embodiment F employ formula (III), wherein  $R_1$  is (w2) and the other substituents are as defined above.

More preferably,  $R_1$  is (w2) and

25 m is 1;

ring C is benzo, pyrido, or thieno;

$R_3$  is selected from the group consisting of -C(O)-H, -C(O)- $Ar_2$ , and -C(O) $CH_2-T_1-R_{11}$ ;

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R<sub>5</sub> is selected from the group consisting of:

-C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is -Ar<sub>3</sub>;

-C(O)O-R<sub>9</sub>, wherein R<sub>9</sub> is -CH<sub>2</sub>-Ar<sub>3</sub>;

-C(O)C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is -Ar<sub>3</sub>;

5 -R<sub>9</sub>, wherein R<sub>9</sub> is a C<sub>1-2</sub> alkyl group

substituted with -Ar<sub>3</sub>; and

-C(O)C(O)-OR<sub>10</sub>, wherein R<sub>10</sub> is -CH<sub>2</sub>Ar<sub>3</sub>;

T<sub>1</sub> is O or S;

10 R<sub>6</sub> is H;

R<sub>8</sub> is selected from the group consisting -C(O)-R<sub>10</sub>,  
-C(O)-CH<sub>2</sub>-OR<sub>10</sub>, and -C(O)CH<sub>2</sub>-N(R<sub>10</sub>)(R<sub>10</sub>), wherein R<sub>10</sub> is  
H, CH<sub>3</sub>, or -CH<sub>2</sub>CH<sub>3</sub>;

15 R<sub>11</sub> is selected from the group consisting of -Ar<sub>4</sub>,  
-(CH<sub>2</sub>)<sub>1-3</sub>-Ar<sub>4</sub>, and -C(O)-Ar<sub>4</sub>;

R<sub>15</sub> is -OH or -OC<sub>1-4</sub> straight or branched alkyl  
group optionally substituted with -Ar<sub>3</sub>, -OH, -OR<sub>9</sub>, or  
-CO<sub>2</sub>H, wherein the R<sub>9</sub> is a -C<sub>1-4</sub> branched or straight  
alkyl group, wherein Ar<sub>3</sub> is morpholinyl or phenyl,  
20 wherein the phenyl is optionally substituted with Q<sub>1</sub>;

Ar<sub>2</sub> is (hh);

Y is O;

25 each Ar<sub>3</sub> cyclic group is independently selected  
from the set consisting of phenyl, naphthyl, thienyl,  
quinolinyl, isoquinolinyl, thiazolyl, benzimidazolyl,  
thienothienyl, thiadiazolyl, benzotriazolyl,  
benzo[b]thiophenyl, benzofuranyl, and indolyl, and said  
cyclic group optionally being singly or multiply  
30 substituted by -Q<sub>1</sub>;

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each Ar<sub>4</sub> cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, naphthyl, pyridinyl, oxazolyl, pyrimidinyl, or indolyl, said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Q<sub>1</sub> is independently selected from the group consisting of -NH<sub>2</sub>, -Cl, -F, -Br, -OH, -R<sub>9</sub>, -NH-R<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or -S(O)<sub>2</sub>-R<sub>9</sub>, -OR<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub>, -OR<sub>9</sub>, -N(R<sub>9</sub>)(R<sub>10</sub>), and



15 wherein each R<sub>9</sub> and R<sub>10</sub> are independently a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub> wherein Ar<sub>3</sub> is phenyl;

20 provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub> group which comprises one or more additional -Ar<sub>3</sub> groups, said additional -Ar<sub>3</sub> groups are not substituted with another -Ar<sub>3</sub>.

Other preferred compounds of embodiment F employ formula (III), wherein R<sub>1</sub> is (e11) and the other substituents are as defined above.

Other preferred compounds of embodiment F employ formula (III), wherein R<sub>1</sub> is (e12) and the other substituents are as defined above.

30 Other preferred compounds of embodiment F employ formula (III) wherein R<sub>1</sub> is (y1) and the other substituents are as defined above.

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Other preferred compounds of embodiment F employ formula (III) wherein  $R_1$  is ( $\gamma_2$ ) and the other substituents are as defined above.

5 Other preferred compounds of embodiment F employ formula (III) wherein  $R_1$  is ( $z$ ) and the other substituents are as defined above.

Other preferred compounds of embodiment F employ formula (III) wherein  $R_1$  is ( $e10$ ),  $X_5$  is CH, and the other substituents are as defined above.

10 Other preferred compounds of embodiment F employ formula (III) wherein  $R_1$  is ( $e10$ ),  $X_5$  is N, and the other substituents are as defined above.

More preferably, in these more preferred compounds,  $R_5$  is selected from the group consisting of:

15        -C(O)- $R_{10}$ ,  
         -C(O)O- $R_9$ , and  
         -C(O)-NH- $R_{10}$ .

Alternatively, in these more preferred compounds,  $R_5$  is selected from the group consisting of:

20        -S(O)<sub>2</sub>- $R_9$ ,  
         -S(O)<sub>2</sub>-NH- $R_{10}$ ,  
         -C(O)-C(O)- $R_{10}$ ,  
         - $R_9$ ,  
         -C(O)-C(O)-OR<sub>10</sub>, and  
25        -C(O)C(O)-N( $R_9$ )( $R_{10}$ ).

Most preferably, in these more preferred compounds,

$m$  is 1;

$R_{13}$  is H or a -C<sub>1-4</sub> straight or branched alkyl

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group optionally substituted with  $-\text{Ar}_3$ ,  $-\text{OH}$ ,  $-\text{OR}_9$ , or  $-\text{CO}_2\text{H}$ , wherein the  $\text{R}_9$  is a  $-\text{C}_{1-4}$  branched or straight alkyl group, wherein  $\text{Ar}_3$  is morpholinyl or phenyl, wherein the phenyl is optionally substituted with  $\text{Q}_1$ ;

5  $\text{R}_{21}$  is  $-\text{H}$  or  $-\text{CH}_3$ ;

$\text{R}_{51}$  is a  $\text{C}_{1-6}$  straight or branched alkyl group optionally substituted with  $\text{Ar}_3$ , wherein  $\text{Ar}_3$  is phenyl, optionally substituted by  $-\text{Q}_1$ ;

10 each  $\text{Ar}_3$  cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl,  
 15 benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by  $-\text{Q}_1$ ;

each  $\text{Q}_1$  is independently selected from the group consisting of  $-\text{NH}_2$ ,  $-\text{Cl}$ ,  $-\text{F}$ ,  $-\text{Br}$ ,  $-\text{OH}$ ,  $-\text{R}_9$ ,  $-\text{NH}-\text{R}_5$   
 20 wherein  $\text{R}_5$  is  $-\text{C}(\text{O})-\text{R}_{10}$  or  $-\text{S}(\text{O})_2-\text{R}_9$ ,  $-\text{OR}_5$  wherein  $\text{R}_5$  is  $-\text{C}(\text{O})-\text{R}_{10}$ ,  $-\text{OR}_9$ ,  $-\text{N}(\text{R}_9)(\text{R}_{10})$ , and



wherein each  $\text{R}_9$  and  $\text{R}_{10}$  are independently a  $-\text{C}_{1-6}$  straight or branched alkyl group optionally substituted with  $\text{Ar}_3$  wherein  $\text{Ar}_3$  is phenyl;

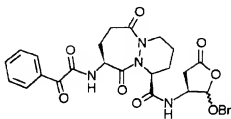
30 provided that when  $-\text{Ar}_3$  is substituted with a  $\text{Q}_1$  group which comprises one or more additional  $-\text{Ar}_3$  groups, said additional  $-\text{Ar}_3$  groups are not substituted

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with another  $-\text{Ar}_3$ .

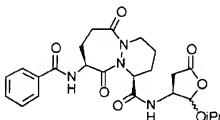
Preferred compounds of embodiment (F) include, but are not limited to:

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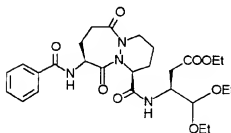


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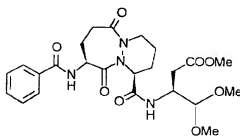
2100a



2100b

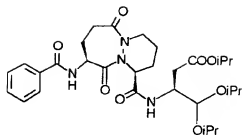


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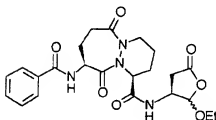


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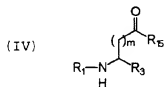
2100d



2100e



The ICE inhibitors of another embodiment (G)  
 5 of this invention are those of formula (IV):



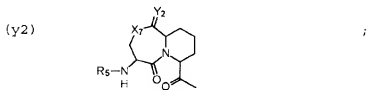
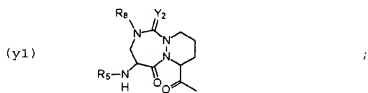
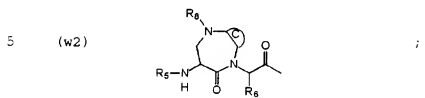
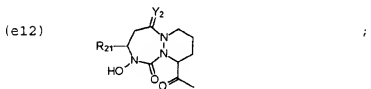
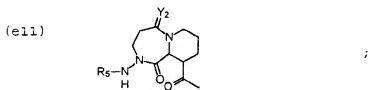
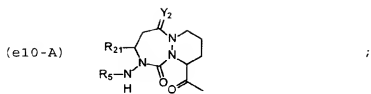
wherein:

m is 1 or 2;

10  $R_1$  is selected from the group consisting of the  
 following formulae:

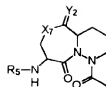


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(z)



; and

ring C is chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

R<sub>3</sub> is selected from the group consisting of:

- CN,
- C(O)-H,
- C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>,
- C(O)-CH<sub>2</sub>-F,
- C=N-O-R<sub>9</sub>, and
- CO-Ar<sub>2</sub>;

each R<sub>5</sub> is independently selected from the group consisting of:

- C(O)-R<sub>10</sub>,
- C(O)O-R<sub>9</sub>,
- C(O)-N(R<sub>10</sub>)(R<sub>10</sub>)
- S(O)<sub>2</sub>-R<sub>9</sub>,
- S(O)<sub>2</sub>-NH-R<sub>10</sub>,
- C(O)-CH<sub>2</sub>-O-R<sub>9</sub>,
- C(O)C(O)-R<sub>10</sub>,
- R<sub>9</sub>,
- H,
- C(O)C(O)-OR<sub>10</sub>, and
- C(O)C(O)-N(R<sub>9</sub>)(R<sub>10</sub>);

Y<sub>2</sub> is H<sub>2</sub> or O;

X<sub>1</sub> is -N(R<sub>8</sub>)- or -O-;

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each  $T_1$  is independently selected from the group consisting of -O-, -S-, -S(O)-, and -S(O)<sub>2</sub>-;

5         $R_6$  is selected from the group consisting of -H and -CH<sub>3</sub>;

$R_8$  is selected from the group consisting of:

10        -C(O)- $R_{10}$ ,  
         -C(O)O- $R_9$ ,  
         -C(O)-NH- $R_{10}$ ,  
         -S(O)<sub>2</sub>- $R_9$ ,  
         -S(O)<sub>2</sub>-NH- $R_{10}$ ,  
         -C(O)-CH<sub>2</sub>-OR<sub>10</sub>,  
         -C(O)C(O)- $R_{10}$ ,  
15        -C(O)-CH<sub>2</sub>-N( $R_{10}$ )( $R_{10}$ ),  
         -C(O)-CH<sub>2</sub>C(O)-O- $R_9$ ,  
         -C(O)-CH<sub>2</sub>C(O)- $R_9$ ,  
         -H, and  
         -C(O)-C(O)-OR<sub>10</sub>;

20        each  $R_9$  is independently selected from the group consisting of -Ar<sub>3</sub> and a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, wherein the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

25        each  $R_{10}$  is independently selected from the group consisting of -H, -Ar<sub>3</sub>, a C<sub>3-6</sub> cycloalkyl group, and a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, wherein the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

30        each  $R_{11}$  is independently selected from the group consisting of:

         -Ar<sub>4</sub>,  
         -(CH<sub>2</sub>)<sub>1-3</sub>-Ar<sub>4</sub>,  
         -H, and

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-C(O)-Ar<sub>4</sub>;

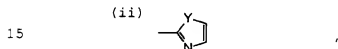
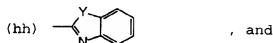
R<sub>15</sub> is selected from the group consisting of -OH, -OAr<sub>3</sub>, -N(H)-OH, and -OC<sub>1-6</sub>, wherein C<sub>1-6</sub> is a straight or branched alkyl group optionally substituted with

5 Ar<sub>3</sub>, -CONH<sub>2</sub>, -OR<sub>5</sub>, -OH, -OR<sub>9</sub>, or -CO<sub>2</sub>H;

each R<sub>21</sub> is independently selected from the group consisting of -H or a -C<sub>1-6</sub> straight or branched alkyl group;

Ar<sub>2</sub> is independently selected from the following

10 group, in which any ring may optionally be singly or multiply substituted by -Q<sub>1</sub> or phenyl, optionally substituted by Q<sub>1</sub>:



wherein each Y is independently selected from the group consisting of O and S;

each Ar<sub>3</sub> is a cyclic group independently selected from the set consisting of an aryl group which contains

20 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, and -NH-,

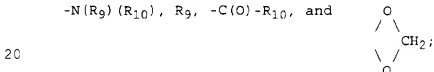
25 -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or

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multiply substituted by  $-Q_1$ ;

each  $Ar_4$  is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from  $-O-$ ,  $-S-$ ,  $-SO-$ ,  $SO_2$ ,  $=N-$ ,  $-NH-$ ,  $-N(R_5)-$ , and  $-N(R_9)-$  said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

each  $Q_1$  is independently selected from the group consisting of  $-NH_2$ ,  $-CO_2H$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-I$ ,  $-NO_2$ ,  $-CN$ ,  $=O$ ,  $-OH$ ,  $-perfluoro\ C_{1-3}\ alkyl$ ,  $R_5$ ,  $-OR_5$ ,  $-NHR_5$ ,  $OR_9$ ,  $-N(R_9)(R_{10})$ ,  $R_9$ ,  $-C(O)-R_{10}$ , and



provided that when  $-Ar_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-Ar_3$  groups, said additional  $-Ar_3$  groups are not substituted with another  $-Ar_3$ ;

Preferred compounds of embodiment G employ formula (IV), wherein  $R_1$  is (w2) and the other substituents are as defined above.

Preferably, when  $R_1$  is (w2):

m is 1;

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ring C is benzo, pyrido, or thieno;

R<sub>5</sub> is selected from the group consisting of:

-C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is -Ar<sub>3</sub>;

-C(O)O-R<sub>9</sub>, wherein R<sub>9</sub> is -CH<sub>2</sub>-Ar<sub>3</sub>;

5 -C(O)C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is -Ar<sub>3</sub>;

-R<sub>9</sub>, wherein R<sub>9</sub> is a C<sub>1-2</sub> alkyl group

substituted with -Ar<sub>3</sub>; and

-C(O)C(O)-OR<sub>10</sub>, wherein R<sub>10</sub> is -CH<sub>2</sub>Ar<sub>3</sub>;

10 R<sub>6</sub> is H;

R<sub>8</sub> is selected from the group consisting -C(O)-R<sub>10</sub>,  
-C(O)-CH<sub>2</sub>-OR<sub>10</sub>, and -C(O)CH<sub>2</sub>-N(R<sub>10</sub>)(R<sub>10</sub>), wherein R<sub>10</sub> is  
H, CH<sub>3</sub>, or -CH<sub>2</sub>CH<sub>3</sub>;

15 R<sub>13</sub> is H or a C<sub>1-4</sub> straight or branched alkyl group  
optionally substituted with Ar<sub>3</sub>, -OH, -OR<sub>9</sub>, -CO<sub>2</sub>H,  
wherein the R<sub>9</sub> is a C<sub>1-4</sub> branched or straight chain  
alkyl group; wherein Ar<sub>3</sub> is morpholinyl or phenyl,  
wherein the phenyl is optionally substituted with Q<sub>1</sub>;

20 Ar<sub>3</sub> is phenyl, naphthyl, thienyl, quinolinyl,  
isoquinolinyl, thiazolyl, benzimidazolyl,  
thienothienyl, thiadiazolyl, benzotriazolyl,  
benzo[b]thiophenyl, benzofuranyl, and indolyl;

25 each Q<sub>1</sub> is independently selected from the group  
consisting of -NH<sub>2</sub>, -Cl, -F, -Br, -OH, -R<sub>9</sub>, -NH-R<sub>5</sub>  
wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or -S(O)<sub>2</sub>-R<sub>9</sub>, -OR<sub>5</sub> wherein R<sub>5</sub> is  
-C(O)-R<sub>10</sub>, -OR<sub>9</sub>, -NHR<sub>9</sub>, and



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wherein each  $R_9$  and  $R_{10}$  are independently a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$  wherein  $Ar_3$  is phenyl;

- 5           provided that when  $-Ar_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-Ar_3$  groups, said additional  $-Ar_3$  groups are not substituted with another  $-Ar_3$ .

- 10           Other preferred compounds of embodiment G employ formula (IV) wherein  $R_1$  is (e10-A) and the other substituents are as defined above.

Other preferred compounds of embodiment G employ formula (IV) wherein  $R_1$  is (e11) and the other substituents are as defined above.

- 15           Other preferred compounds of embodiment G employ formula (IV) wherein  $R_1$  is (e12) and the other substituents are as defined above.

- 20           Other preferred compounds of embodiment G employ formula (IV) wherein  $R_1$  is (y1) and the other substituents are as defined above.

Other preferred compounds of embodiment G employ formula (IV) wherein  $R_1$  is (y2) and the other substituents are as defined above.

- 25           Other preferred compounds of embodiment G employ formula (IV) wherein  $R_1$  is (z) and the other substituents are as defined above.

More preferred compounds of embodiment G are those wherein  $R_3$  is  $-CO-Ar_2$ .

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Most preferably, when  $R_3$  is  $-\text{CO}-\text{Ar}_2$ ,  $Y$  is  $O$ .

Other more preferred compounds are those wherein  $R_3$  is  $-\text{C}(O)-\text{CH}_2-\text{T}_1-\text{R}_{11}$  and  $\text{R}_{11}$  is  $-(\text{CH}_2)_{1-3}-\text{Ar}_4$ .

Most preferably, when  $R_3$  is  $-\text{C}(O)-\text{CH}_2-\text{T}_1-\text{R}_{11}$   
5 and  $\text{R}_{11}$  is  $-(\text{CH}_2)_{1-3}-\text{Ar}_4$ ,  $\text{T}_1$  is  $O$ .

Other more preferred compounds are those wherein:

$R_3$  is  $-\text{C}(O)-\text{CH}_2-\text{T}_1-\text{R}_{11}$ ;

$\text{T}_1$  is  $O$ ; and

$\text{R}_{11}$  is  $-\text{C}(O)-\text{Ar}_4$ .

Other more preferred compounds are those wherein  
10  $R_3$  is  $-\text{C}(O)-\text{H}$ .

Other more preferred compounds are those wherein  
 $R_3$  is  $-\text{CO}-\text{CH}_2-\text{T}_1-\text{R}_{11}$  and  $\text{R}_{11}$  is  $-\text{Ar}_4$ .

More preferably, when  $R_3$  is  $-\text{CO}-\text{CH}_2-\text{T}_1-\text{R}_{11}$  and  
15  $\text{R}_{11}$  is  $-\text{Ar}_4$ ,  $\text{T}_1$  is  $O$  or  $S$ .

More preferably, when  $\text{R}_1$  is  $\{e11\}$ ,  $\{e12\}$ ,  $\{y1\}$ ,  
 $\{y2\}$ ,  $\{z\}$ ,  $\{e10-A\}$ , and  $\{e10-B\}$ ,  $\text{R}_5$  is selected from  
the group consisting of:

$-\text{C}(O)-\text{R}_{10}$ ,  
20  $-\text{C}(O)O-\text{R}_9$ , and  
 $-\text{C}(O)-\text{NH}-\text{R}_{10}$ .

Alternatively, when  $\text{R}_1$  is  $\{e11\}$ ,  $\{e12\}$ ,  $\{y1\}$ ,  
 $\{y2\}$ ,  $\{z\}$ ,  $\{e10-A\}$ , and  $\{e10-B\}$ ,  $\text{R}_5$  is selected from  
the group consisting of:

$-\text{S}(O)_2-\text{R}_9$ ,  
25  $-\text{S}(O)_2-\text{NH}-\text{R}_{10}$ ,  
 $-\text{C}(O)-\text{C}(O)-\text{R}_{10}$ ,  
 $-\text{R}_9$ ,



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-C(O)-C(O)-OR<sub>10</sub>, and  
-C(O)-C(O)-N(R<sub>9</sub>)(R<sub>10</sub>).

More preferably, R<sub>5</sub> is -C(O)-C(O)-R<sub>10</sub>.

Alternatively, R<sub>5</sub> is -C(O)-C(O)-OR<sub>10</sub>.

5 Most preferably, when R<sub>1</sub> is (e11), (e12), (y1), (y2),  
(z), (e10-A), and (e10-B),:

m is 1;

R<sub>21</sub> is -H or -CH<sub>3</sub>;

R<sub>51</sub> is a C<sub>1-6</sub> straight or branched alkyl group  
10 optionally substituted with Ar<sub>3</sub>, wherein the Ar<sub>3</sub> cyclic  
group is phenyl, said cyclic group optionally being  
multiply or singly substituted by -Q<sub>1</sub>;

each Ar<sub>3</sub> cyclic group is independently selected  
from the set consisting of phenyl, naphthyl, thienyl,  
15 quinoliny, isoquinoliny, pyrazolyl, thiazolyl,  
isoxazolyl, benzotriazolyl, benzimidazolyl,  
thienothienyl, imidazolyl, thiadiazolyl,  
benzo[b]thiophenyl, pyridyl, benzofuranyl, or indolyl,  
and said cyclic group optionally being singly or  
20 multiply substituted by -Q<sub>1</sub>;

each Q<sub>1</sub> is independently selected from the group  
consisting of -NH<sub>2</sub>, -Cl, -F, -Br, -OH, -R<sub>9</sub>, -NH-R<sub>5</sub>  
wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or -S(O)<sub>2</sub>-R<sub>9</sub>, -OR<sub>5</sub> wherein R<sub>5</sub> is  
25 -C(O)-R<sub>10</sub>, -OR<sub>9</sub>, -N(R<sub>9</sub>)(R<sub>10</sub>), and



30

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wherein each  $R_9$  and  $R_{10}$  are independently a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$ , wherein the  $Ar_3$  cyclic group is phenyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

provided that when  $-Ar_3$  is substituted with a  $-Q_1$  group which comprises one or more additional  $-Ar_3$  groups, said additional  $-Ar_3$  groups are not substituted with another  $-Ar_3$ .

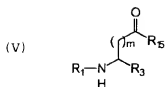
More preferably, in these more preferred compounds, the  $Ar_3$  cyclic group is selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ .

Compounds in a preferred form of embodiment G are those wherein  $R_{21}$  is H and the other substituents are as defined above.

Compounds in another preferred form of embodiment G are those wherein  $R_{21}$  is  $CH_3$  and the other substituents are as defined above.

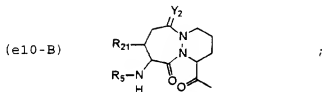
The ICE inhibitors of another embodiment (H) of this invention are those of formula (V):

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wherein:

m is 1 or 2;

5  $\text{R}_1$  is: $\text{R}_3$  is selected from the group consisting of:

- CN,
- C(O)-H,
- 10 -C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>,
- C(O)-CH<sub>2</sub>-F,
- C=N-O-R<sub>9</sub>, and
- CO-Ar<sub>2</sub>;

each  $\text{R}_5$  is independently selected from the group  
 15 consisting of:

- C(O)-R<sub>10</sub>,
- C(O)O-R<sub>9</sub>,
- C(O)-N(R<sub>10</sub>)(R<sub>10</sub>)
- S(O)<sub>2</sub>-R<sub>9</sub>,
- 20 -S(O)<sub>2</sub>-NH-R<sub>10</sub>,
- C(O)-CH<sub>2</sub>-O-R<sub>9</sub>,
- C(O)C(O)-R<sub>10</sub>,
- R<sub>9</sub>,
- H, and
- 25 -C(O)C(O)-N(R<sub>9</sub>)(R<sub>10</sub>), and
- C(O)C(O)-OR<sub>10</sub>;

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$Y_2$  is  $H_2$  or  $O$ ;

each  $T_1$  is independently selected from the group consisting of  $-O-$ ,  $-S-$ ,  $-S(O)-$ , and  $-S(O)_2-$ ;

- 5  $R_8$  is selected from the group consisting of:
- C(O)- $R_{10}$ ,
  - C(O)O- $R_9$ ,
  - C(O)-NH- $R_{10}$ ,
  - S(O) $_2$ - $R_9$ ,
  - 10 -S(O) $_2$ -NH- $R_{10}$ ,
  - C(O)-CH $_2$ -OR $_{10}$ ,
  - C(O)C(O)- $R_{10}$ ,
  - C(O)-CH $_2$ -N( $R_{10}$ )( $R_{10}$ ),
  - C(O)-CH $_2$ C(O)-O- $R_9$ ,
  - 15 -C(O)-CH $_2$ C(O)- $R_9$ ,
  - H, and
  - C(O)-C(O)-OR $_{10}$ ;

- each  $R_9$  is independently selected from the group consisting of  $-Ar_3$  and a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$ , wherein
- 20 the  $-C_{1-6}$  alkyl group is optionally unsaturated;

- each  $R_{10}$  is independently selected from the group consisting of  $-H$ ,  $-Ar_3$ , a  $C_{3-6}$  cycloalkyl group, and a  $-C_{1-6}$  straight or branched alkyl group optionally
- 25 substituted with  $Ar_3$ , wherein the  $-C_{1-6}$  alkyl group is optionally unsaturated;

each  $R_{11}$  is independently selected from the group consisting of:

- 30  $-Ar_4$ ,
- (CH $_2$ ) $_{1-3}$ - $Ar_4$ ,
  - H, and
  - C(O)- $Ar_4$ ;

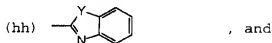
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R<sub>15</sub> is selected from the group consisting of -OH, -OAr<sub>3</sub>, -N(H)-OH, and -OC<sub>1-6</sub>, wherein C<sub>1-6</sub> is a straight or branched alkyl group optionally substituted with Ar<sub>3</sub>,

5 -CONH<sub>2</sub>, -OR<sub>5</sub>, -OH, -OR<sub>9</sub>, or -CO<sub>2</sub>H;

R<sub>21</sub> is -CH<sub>3</sub>;

Ar<sub>2</sub> is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by -Q<sub>1</sub> or phenyl, optionally substituted by Q<sub>1</sub>:



15 wherein each Y is independently selected from the group consisting of O and S;

each Ar<sub>3</sub> is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, and -NH-, -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Ar<sub>4</sub> is a cyclic group independently selected

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from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said

5 heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, -NH-, -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings,

10 and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Q<sub>1</sub> is independently selected from the group consisting of -NH<sub>2</sub>, -CO<sub>2</sub>H, -Cl, -F, -Br, -I, -NO<sub>2</sub>, -CN, =O, -OH, -perfluoro C<sub>1-3</sub> alkyl, R<sub>5</sub>, -OR<sub>5</sub>, -NHR<sub>5</sub>, OR<sub>9</sub>,

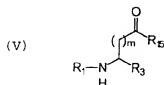
15 -N(R<sub>9</sub>)(R<sub>10</sub>), R<sub>9</sub>, -C(O)-R<sub>10</sub>, and



20 provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub> group which comprises one or more additional -Ar<sub>3</sub> groups, said additional -Ar<sub>3</sub> groups are not substituted with another -Ar<sub>3</sub>;

Compounds of another form of embodiment (I)

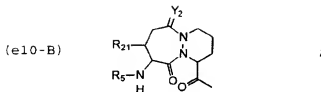
25 (form 1) are those of formula (V):



wherein:

m is 1 or 2;

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 $R_1$  is: $R_3$  is selected from the group consisting of:

-CN,  
 -C(O)-H,  
 -C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>,  
 -C(O)-CH<sub>2</sub>-F,  
 -C=N-O-R<sub>9</sub>, and  
 -CO-Ar<sub>2</sub>;

each  $R_5$  is -C(O)C(O)-OR<sub>10</sub>; $Y_2$  is H<sub>2</sub> or O;

each T<sub>1</sub> is independently selected from the group  
 consisting of -O-, -S-, -S(O)-, and -S(O)<sub>2</sub>-;

 $R_8$  is selected from the group consisting of:

-C(O)-R<sub>10</sub>,  
 -C(O)O-R<sub>9</sub>,  
 -C(O)-NH-R<sub>10</sub>,  
 -S(O)<sub>2</sub>-R<sub>9</sub>,  
 -S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
 -C(O)-CH<sub>2</sub>-OR<sub>10</sub>,  
 -C(O)C(O)-R<sub>10</sub>,  
 -C(O)-CH<sub>2</sub>-N(R<sub>10</sub>)(R<sub>10</sub>),  
 -C(O)-CH<sub>2</sub>C(O)-O-R<sub>9</sub>,  
 -C(O)-CH<sub>2</sub>C(O)-R<sub>9</sub>,  
 -H, and  
 -C(O)-C(O)-OR<sub>10</sub>;

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each  $R_9$  is independently selected from the group consisting of  $-Ar_3$  and a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$ , wherein the  $-C_{1-6}$  alkyl group is optionally unsaturated;

5 each  $R_{10}$  is independently selected from the group consisting of  $-H$ ,  $-Ar_3$ , a  $C_{3-6}$  cycloalkyl group, and a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$ , wherein the  $-C_{1-6}$  alkyl group is optionally unsaturated;

10 each  $R_{11}$  is independently selected from the group consisting of:

$-Ar_4$ ,  
 $-(CH_2)_{1-3}-Ar_4$ ,  
 $-H$ , and  
15  $-C(O)-Ar_4$ ;

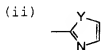
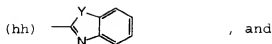
$R_{15}$  is selected from the group consisting of  $-OH$ ,  $-OAr_3$ ,  $-N(H)-OH$ , and  $-OC_{1-6}$ , wherein  $C_{1-6}$  is a straight or branched alkyl group optionally substituted with  $Ar_3$ ,  $-CONH_2$ ,  $-OR_5$ ,  $-OH$ ,  $-OR_9$ , or  $-CO_2H$ ;

20 each  $R_{21}$  is independently selected from the group consisting of  $-H$  or a  $-C_{1-6}$  straight or branched alkyl group;

$Ar_2$  is independently selected from the following group, in which any ring may optionally be singly or  
25 multiply substituted by  $-Q_1$  or phenyl, optionally substituted by  $Q_1$ :



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5        wherein each Y is independently selected from the group consisting of O and S;

10        each Ar<sub>3</sub> is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, and -NH-, -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

20        each Ar<sub>4</sub> is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, -NH-, -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

30        each Q<sub>1</sub> is independently selected from the group

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consisting of  $-NH_2$ ,  $-CO_2H$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-I$ ,  $-NO_2$ ,  $-CN$ ,  
 $=O$ ,  $-OH$ ,  $-perfluoro\ C_{1-3}\ alkyl$ ,  $R_5$ ,  $-OR_5$ ,  $-NHR_5$ ,  $OR_9$ ,  
 $-N(R_9)(R_{10})$ ,  $R_9$ ,  $-C(O)-R_{10}$ , and

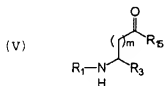
5



provided that when  $-Ar_3$  is substituted with a  $Q_1$   
 group which comprises one or more additional  $-Ar_3$   
 groups, said additional  $-Ar_3$  groups are not substituted  
 with another  $-Ar_3$ ;

Alternatively, compounds of this form of  
 embodiment I (form 2) are those wherein  $R_{21}$  is  $-CH_3$ .

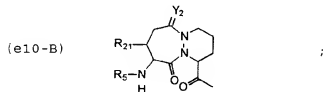
Compounds of another form of embodiment (J) (form  
 1) are those of formula (V):



wherein:

$m$  is 1 or 2;

$R_1$  is:



$R_3$  is selected from the group consisting of:

$-CN$ ,  
 $-C(O)-H$ ,

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-C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>,  
 -C(O)-CH<sub>2</sub>-F,  
 -C=N-O-R<sub>9</sub>, and  
 -CO-Ar<sub>2</sub>;

5           each R<sub>5</sub> is independently selected from the  
 group consisting of:  
           -C(O)-R<sub>10</sub>,  
           -C(O)O-R<sub>9</sub>,  
           -C(O)-N(R<sub>10</sub>)(R<sub>10</sub>)  
 10          -S(O)<sub>2</sub>-R<sub>9</sub>,  
           -S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
           -C(O)-CH<sub>2</sub>-O-R<sub>9</sub>,  
           -C(O)C(O)-R<sub>10</sub>,  
           -R<sub>9</sub>,  
 15          -H,  
           -C(O)C(O)-OR<sub>10</sub>, and  
           -C(O)C(O)-N(R<sub>9</sub>)(R<sub>10</sub>);

Y<sub>2</sub> is H<sub>2</sub> or O;

20           each T<sub>1</sub> is independently selected from the group  
 consisting of -O-, -S-, -S(O)-, and -S(O)<sub>2</sub>-;

          R<sub>9</sub> is selected from the group consisting of:  
           -C(O)-R<sub>10</sub>,  
           -C(O)O-R<sub>9</sub>,  
 25          -C(O)-NH-R<sub>10</sub>,  
           -S(O)<sub>2</sub>-R<sub>9</sub>,  
           -S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
           -C(O)-CH<sub>2</sub>-OR<sub>10</sub>,  
           -C(O)C(O)-R<sub>10</sub>,  
 30          -C(O)-CH<sub>2</sub>-N(R<sub>10</sub>)(R<sub>10</sub>),  
           -C(O)-CH<sub>2</sub>C(O)-O-R<sub>9</sub>,  
           -C(O)-CH<sub>2</sub>C(O)-R<sub>9</sub>,  
           -H,

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-C(O)-C(O)-OR<sub>10</sub>, and  
-C(O)-C(O)-N(R<sub>9</sub>)(R<sub>10</sub>);

each R<sub>9</sub> is independently selected from the group consisting of -Ar<sub>3</sub> and a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, wherein the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

each R<sub>10</sub> is independently selected from the group consisting of -H, -Ar<sub>3</sub>, a C<sub>3-6</sub> cycloalkyl group, and a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, wherein the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

each R<sub>11</sub> is independently selected from the group consisting of:

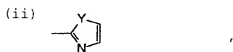
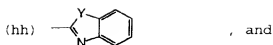
-Ar<sub>4</sub>,  
-(CH<sub>2</sub>)<sub>1-3</sub>-Ar<sub>4</sub>,  
-H, and  
-C(O)-Ar<sub>4</sub>;

R<sub>15</sub> is selected from the group consisting of -OH, -OAr<sub>3</sub>, -N(H)-OH, and -OC<sub>1-6</sub>, wherein C<sub>1-6</sub> is a straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, -CONH<sub>2</sub>, -OR<sub>5</sub>, -OH, -OR<sub>6</sub>, or -CO<sub>2</sub>H;

each R<sub>21</sub> is independently selected from the group consisting of -H or a -C<sub>1-6</sub> straight or branched alkyl group;

Ar<sub>2</sub> is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by -Q<sub>1</sub> or phenyl, optionally substituted by Q<sub>1</sub>:

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5        wherein each Y is independently selected from the group consisting of O and S;

each Ar<sub>3</sub> is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, and -NH-, -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Ar<sub>4</sub> is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, -NH-, -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

30        each Q<sub>1</sub> is independently selected from the group

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consisting of  $-NH_2$ ,  $-CO_2H$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-I$ ,  $-NO_2$ ,  $-CN$ ,  
 $=O$ ,  $-OH$ ,  $-perfluoro\ C_{1-3}\ alkyl$ ,  $R_5$ ,  $-OR_5$ ,  $-NHR_5$ ,  $OR_9$ ,  
 $-N(R_9)(R_{10})$ ,  $R_9$ ,  $-C(O)-R_{10}$ , and

5



provided that when  $-Ar_3$  is substituted with a  $Q_1$   
 group which comprises one or more additional  $-Ar_3$   
 10 groups, said additional  $-Ar_3$  groups are not substituted  
 with another  $-Ar_3$ ;

provided that when:

$m$  is 1;

$R_1$  is  $(e10)$ ;

15  $X_5$  is  $CH$ ;

$R_{15}$  is  $-OH$ ;

$R_{21}$  is  $-H$ ; and

$Y_2$  is  $O$  and  $R_3$  is  $-C(O)-H$ , then  $R_5$  cannot be:

$-C(O)-R_{10}$ , wherein  $R_{10}$  is  $-Ar_3$  and the  $Ar_3$  cyclic  
 20 group is phenyl, unsubstituted by  $-Q_1$ , 4-  
 (carboxymethoxy)phenyl, 2-fluorophenyl, 2-pyridyl, N-  
 (4-methylpiperazino)methylphenyl, or

$-C(O)-OR_9$ , wherein  $R_9$  is  $-CH_2-Ar_3$ , and the  $Ar_3$   
 cyclic group is phenyl, unsubstituted by  $-Q_1$ ; and when

25  $Y_2$  is  $O$ ,  $R_3$  is  $-C(O)-CH_2-T_1-R_{11}$ ,  $T_1$  is  $O$ , and  $R_{11}$   
 is  $Ar_4$ , wherein the  $Ar_4$  cyclic group is 5-(1-(4-  
 chlorophenyl)-3-trifluoromethyl)pyrazolyl), then  $R_5$   
 cannot be:

$-C(O)-R_{10}$ , wherein  $R_{10}$  is  $-Ar_3$  and the  $Ar_3$  cyclic  
 30 group is 4-(dimethylaminomethyl)phenyl, phenyl, 4-  
 (carboxymethylthio)phenyl, 4-(carboxyethylthio)phenyl,  
 4-(carboxyethyl)phenyl, 4-(carboxypropyl)phenyl, 2-

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fluorophenyl, 2-pyridyl, N-(4-methylpiperazino)methylphenyl, or

-C(O)-OR<sub>9</sub>, wherein R<sub>9</sub> is -CH<sub>2</sub>-Ar<sub>3</sub> and the Ar<sub>3</sub> cyclic group is phenyl;

- 5 and when R<sub>11</sub> is Ar<sub>4</sub>, wherein the Ar<sub>4</sub> cyclic group is 5-(1-phenyl-3-trifluoromethyl)pyrazolyl, then R<sub>5</sub> cannot be:

-C(O)-OR<sub>9</sub>, wherein R<sub>9</sub> is -CH<sub>2</sub>-Ar<sub>3</sub>, and the Ar<sub>3</sub> cyclic group is phenyl;

- 10 and when R<sub>11</sub> is Ar<sub>4</sub>, wherein the Ar<sub>4</sub> cyclic group is 5-(1-(2-pyridyl)-3-trifluoromethyl)pyrazolyl, then R<sub>5</sub> cannot be:

-C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is -Ar<sub>3</sub> and the Ar<sub>3</sub> cyclic group is 4-(dimethylaminomethyl)phenyl, or

- 15 -C(O)-OR<sub>9</sub>, wherein R<sub>9</sub> is -CH<sub>2</sub>-Ar<sub>3</sub>, and the Ar<sub>3</sub> cyclic group is phenyl, unsubstituted by -Q<sub>1</sub>,; and when

Y<sub>2</sub> is O, R<sub>3</sub> is -C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>, T<sub>1</sub> is O, and R<sub>11</sub> is -C(O)-Ar<sub>4</sub>, wherein the Ar<sub>4</sub> cyclic group is 2,5-dichlorophenyl, then R<sub>5</sub> cannot be:

- 20 -C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is -Ar<sub>3</sub> and the Ar<sub>3</sub> cyclic group is 4-(dimethylaminomethyl)phenyl, 4-(N-morpholinomethyl)phenyl, 4-(N-methylpiperazino)methylphenyl, 4-(N-methylimidazolylmethyl)phenyl, 5-benzimidazolyl, 5-benzotriazolyl, N-carboethoxy-5-benzotriazolyl, N-carboethoxy-5-benzimidazolyl, or

-C(O)-OR<sub>9</sub>, wherein R<sub>9</sub> is -CH<sub>2</sub>-Ar<sub>3</sub>, and the Ar<sub>3</sub> cyclic group is phenyl, unsubstituted by -Q<sub>1</sub>,; and when

- 30 is Y<sub>2</sub> is H<sub>2</sub>, R<sub>3</sub> is -C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>, T<sub>1</sub> is O, and R<sub>11</sub> is -C(O)-Ar<sub>4</sub>, wherein the Ar<sub>4</sub> cyclic group is 2,5-dichlorophenyl, then R<sub>5</sub> cannot be:

-C(O)-OR<sub>9</sub>, wherein R<sub>9</sub> is -CH<sub>2</sub>-Ar<sub>3</sub> and the Ar<sub>3</sub>

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cyclic group is phenyl.

Compounds of another form of embodiment J (form 2) are those wherein  $R_{21}$  is  $-\text{CH}_3$ .

Compounds of another form of embodiment J (form 3) are those wherein  $R_5$  is  $-\text{C}(\text{O})-\text{C}(\text{O})-\text{OR}_{10}$ .

Compounds of another form of embodiment J (form 4) are those wherein  $R_5$  is  $-\text{C}(\text{O})-\text{C}(\text{O})-\text{OR}_{10}$  and  $R_{21}$  is  $-\text{CH}_3$ .

Preferred compounds of embodiments H, I, and J employ formula (V), wherein  $R_3$  is  $-\text{CO}-\text{Ar}_2$ .

More preferably, when  $R_3$  is  $-\text{CO}-\text{Ar}_2$  Y is O.

Preferred compounds of embodiments H, I, and J employ formula (V), wherein  $R_3$  is  $-\text{C}(\text{O})-\text{CH}_2-\text{T}_1-\text{R}_{11}$  and  $\text{R}_{11}$  is  $-(\text{CH}_2)_{1-3}-\text{Ar}_4$ .

More preferably, when  $R_3$  is  $-\text{C}(\text{O})-\text{CH}_2-\text{T}_1-\text{R}_{11}$  and  $\text{R}_{11}$  is  $-(\text{CH}_2)_{1-3}-\text{Ar}_4$ ,  $\text{T}_1$  is O.

Preferred compounds of embodiments H, I, and J employ formula (V), wherein  $R_3$  is  $-\text{C}(\text{O})-\text{CH}_2-\text{T}_1-\text{R}_{11}$ ,  $\text{T}_1$  is O, and  $\text{R}_{11}$  is  $-\text{C}(\text{O})-\text{Ar}_4$ .

Preferred compounds of embodiments H, I, and J employ formula (V), wherein  $R_3$  is  $-\text{C}(\text{O})-\text{H}$ .

Preferred compounds of embodiments H, I, and J employ formula (V), wherein  $R_3$  is  $-\text{CO}-\text{CH}_2-\text{T}_1-\text{R}_{11}$  and  $\text{R}_{11}$  is  $-\text{Ar}_4$ .

More preferably, when  $R_3$  is  $-\text{CO}-\text{CH}_2-\text{T}_1-\text{R}_{11}$  and



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$R_{11}$  is  $-Ar_4$ ,  $T_1$  is O or S.

More preferred compounds of embodiments H and J (forms 1 and 2) are those wherein  $R_5$  is selected from the group consisting of:

- 5         $-C(O)-R_{10}$ ,  
          $-C(O)O-R_9$ , and  
          $-C(O)-NH-R_{10}$ .

Alternatively, more preferred compounds of embodiments H and J (forms 1 and 2) are those wherein  $R_5$  is selected from the group consisting of:

- 10         $-S(O)_2-R_9$ ,  
          $-S(O)_2-NH-R_{10}$ ,  
          $-C(O)-C(O)-R_{10}$ ,  
          $-R_9$ ,  
15         $-C(O)-C(O)-OR_{10}$ , and  
          $-C(O)-C(O)-N(R_9)(R_{10})$ .

Most preferably,  $R_5$  is  $-C(O)-C(O)-R_{10}$ .

Alternatively,  $R_5$  is  $-C(O)-C(O)-OR_{10}$ .

20        More preferred compounds of embodiments H, I (form 2), and J (forms 2 and 4) are those wherein:

         m is 1;

25         $Y_2$  is O;

$R_{15}$  is  $-OH$  or  $-OC_{1-4}$  straight or branched alkyl group optionally substituted with  $Ar_3$ ,  $-OH$ ,  $-OR_9$ ,  $-CO_2H$ ,  
30        wherein the  $R_9$  is a  $C_{1-4}$  branched or straight chain alkyl group; wherein  $Ar_3$  is morpholinyl or phenyl, wherein the phenyl is optionally substituted with  $Q_1$ ;

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Ar<sub>2</sub> is (hh);

Y is O, and

5 each Ar<sub>3</sub> cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or  
10 multiply substituted by -Q<sub>1</sub>;

each Ar<sub>4</sub> cyclic group is independently selected from the group consisting of phenyl, tetrazolyl, pyridyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or  
15 multiply substituted by -Q<sub>1</sub>;

each Q<sub>1</sub> is independently selected from the group consisting of -NH<sub>2</sub>, -Cl, -F, -Br, -OH, -R<sub>9</sub>, -NH-R<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or -S(O)<sub>2</sub>-R<sub>9</sub>, -OR<sub>5</sub> wherein R<sub>5</sub> is  
20 -C(O)-R<sub>10</sub>, -OR<sub>9</sub>, -N(R<sub>9</sub>)(R<sub>10</sub>), and



25 wherein each R<sub>9</sub> and R<sub>10</sub> are independently a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub> wherein the Ar<sub>3</sub> cyclic group is phenyl, and said cyclic group optionally being singly or multiply  
30 substituted by -Q<sub>1</sub>;

provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub> group which comprises one or more additional -Ar<sub>3</sub> groups, said additional -Ar<sub>3</sub> groups are not substituted

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with another  $-Ar_3$ .

More preferred compounds of embodiments I (form 1), and J (form 3) are those wherein:

m is 1;

5  $R_{21}$  is  $-H$  or  $-CH_3$ ;

$R_{51}$  is a  $C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$ , wherein the  $Ar_3$  cyclic group is phenyl, said cyclic group optionally being multiply or singly substituted by  $-Q_1$ ;

10 each  $Ar_3$  cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinoliny, isoquinoliny, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl,  
15 benzo[b]thiophenyl, pyridyl, benzofuranyl, or indolyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

each  $Q_1$  is independently selected from the group consisting of  $-NH_2$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-OH$ ,  $-R_9$ ,  $-NH-R_5$   
20 wherein  $R_5$  is  $-C(O)-R_{10}$  or  $-S(O)_2-R_9$ ,  $-OR_5$  wherein  $R_5$  is  $-C(O)-R_{10}$ ,  $-OR_9$ ,  $-N(R_9)(R_{10})$ , and



25

wherein each  $R_9$  and  $R_{10}$  are independently a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$ , wherein the  $Ar_3$  cyclic group is phenyl, and  
30 said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

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provided that when  $-Ar_3$  is substituted with a  $-Q_1$  group which comprises one or more additional  $-Ar_3$  groups, said additional  $-Ar_3$  groups are not substituted with another  $-Ar_3$ .

Preferably, in these more preferred compounds the  $Ar_3$  cyclic group is selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ .

Preferred compounds of embodiments H, and J (forms 1 and 1) are those wherein:

$R_3$  is  $-C(O)-CH_2-T_1-R_{11}$ ;

$T_1$  is O; and

$R_{11}$  is  $-C(O)-Ar_4$ , wherein the  $Ar_4$  cyclic group is selected from the set consisting of tetrazolyl, pyridyl, oxazolyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ .

Preferred compounds of embodiments H, I, and J employ formula (V), wherein  $R_3$  is  $-CO-CH_2-T_1-R_{11}$ ,  $R_{11}$  is  $-Ar_4$ , wherein the  $Ar_4$  cyclic group is pyridyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ .

Preferred compounds of embodiment J (form 1) are those wherein:

$R_3$  is  $-C(O)-H$ , and

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R<sub>5</sub> is -C(O)-R<sub>10</sub>, wherein:

R<sub>10</sub> is Ar<sub>3</sub>, wherein the Ar<sub>3</sub> cyclic group is phenyl optionally being singly or multiply substituted by:

-F,

5 -Cl,

-N(H)-R<sub>5</sub>, wherein -R<sub>5</sub> is -H or -C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, wherein Ar<sub>3</sub> is phenyl,

10 -N(R<sub>9</sub>)(R<sub>10</sub>), wherein R<sub>9</sub> and R<sub>10</sub> are independently a -C<sub>1-4</sub> straight or branched alkyl group, or

-O-R<sub>5</sub>, wherein R<sub>5</sub> is H or a -C<sub>1-4</sub> straight or branched alkyl group.

15 More preferably, Ar<sub>3</sub> is phenyl being optionally singly or multiply substituted at the 3- or 5-position by -Cl or at the 4-position by -NH-R<sub>5</sub>, -N(R<sub>9</sub>)(R<sub>10</sub>), or -O-R<sub>5</sub>.

Other more preferred compounds of embodiment J (form 1) are those wherein:

R<sub>3</sub> is -C(O)-H;

20 R<sub>5</sub> is -C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is Ar<sub>3</sub> and the Ar<sub>3</sub> cyclic group is selected from the group consisting of indolyl, benzimidazolyl, thienyl, and benzo[b]thiophenyl, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

25 Other more preferred compounds of embodiment J (form 1) are those wherein:

R<sub>3</sub> is -C(O)-H;

R<sub>5</sub> is -C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is Ar<sub>3</sub> and the Ar<sub>3</sub>

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cyclic group is selected from quinolyl and isoquinolyl, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>.

Other more preferred compounds of embodiment J  
5 (form 1) are those wherein:

R<sub>3</sub> is -C(O)-H;

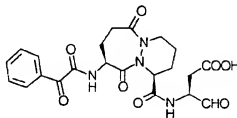
R<sub>5</sub> is -C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is Ar<sub>3</sub> and the Ar<sub>3</sub>  
cyclic group is phenyl, substituted by

10

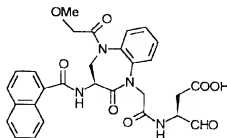


Preferred compounds of embodiment (J)  
15 include, but are not limited to:

2002

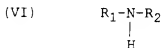


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The ICE inhibitors of another embodiment (K) of this invention are those of formula:

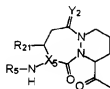


5

wherein:

$R_1$  is:

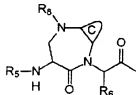
(e10)



, or

10

(w2)

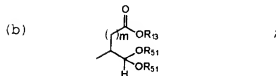
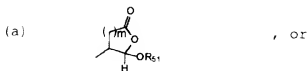


;

C is a ring chosen from the set consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl; the ring optionally being  
15 singly or multiply substituted by  $-Q_1$ ;

$R_2$  is:

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m is 1 or 2;

5 each  $R_5$  is independently selected from the group consisting of:

- C(O)- $R_{10}$ ,
- C(O)O- $R_9$ ,
- C(O)-N( $R_{10}$ )( $R_{10}$ )
- 10 -S(O)<sub>2</sub>- $R_9$ ,
- S(O)<sub>2</sub>-NH- $R_{10}$ ,
- C(O)-CH<sub>2</sub>-O- $R_9$ ,
- C(O)C(O)- $R_{10}$ ,
- $R_9$ ,
- 15 -H,
- C(O)C(O)-OR<sub>10</sub>, and
- C(O)C(O)-N( $R_9$ )( $R_{10}$ );

$X_5$  is CH or N;

20

$Y_2$  is H<sub>2</sub> or O;

$R_6$  is selected from the group consisting of -H and -CH<sub>3</sub>;

25

$R_8$  is selected from the group consisting of:



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-C(O)-R<sub>10</sub>,  
 -C(O)O-R<sub>9</sub>,  
 -C(O)-N(H)-R<sub>10</sub>,  
 -S(O)<sub>2</sub>-R<sub>9</sub>,  
 5       -S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
 -C(O)-CH<sub>2</sub>-OR<sub>10</sub>,  
 -C(O)C(O)-R<sub>10</sub>;  
 -C(O)-CH<sub>2</sub>N(R<sub>10</sub>)(R<sub>10</sub>),  
 -C(O)-CH<sub>2</sub>C(O)-O-R<sub>9</sub>,  
 10       -C(O)-CH<sub>2</sub>C(O)-R<sub>9</sub>,  
 -H, and  
 -C(O)-C(O)-OR<sub>10</sub>;

each R<sub>9</sub> is independently selected from the group  
 consisting of -Ar<sub>3</sub> and a -C<sub>1-6</sub> straight or branched  
 15       alkyl group optionally substituted with Ar<sub>3</sub>, wherein  
 the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

each R<sub>10</sub> is independently selected from the group  
 consisting of -H, -Ar<sub>3</sub>, a -C<sub>3-6</sub> cycloalkyl group, and a  
 -C<sub>1-6</sub> straight or branched alkyl group optionally  
 20       substituted with Ar<sub>3</sub>, wherein the -C<sub>1-6</sub> alkyl group is  
 optionally unsaturated;

R<sub>13</sub> is selected from the group consisting of H,  
 Ar<sub>3</sub>, and a -C<sub>1-6</sub> straight or branched alkyl group  
 optionally substituted with Ar<sub>3</sub>, -CONH<sub>2</sub>, -OR<sub>5</sub>, -OH,  
 25       -OR<sub>9</sub>, or -CO<sub>2</sub>H;

each R<sub>51</sub> is independently selected from the group  
 consisting of R<sub>9</sub>, -C(O)-R<sub>9</sub>, -C(O)-N(H)-R<sub>9</sub>, or each R<sub>51</sub>  
 taken together forms a saturated 4-8 member carbocyclic  
 ring or heterocyclic ring containing -O-, -S-, or -NH-;

- 204 -

each R<sub>21</sub> is independently selected from the group consisting of -H or a -C<sub>1-6</sub> straight or branched alkyl group;

5 each Ar<sub>3</sub> is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said  
 10 heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted  
 15 by -Q<sub>1</sub>;

each Q<sub>1</sub> is independently selected from the group consisting of -NH<sub>2</sub>, -CO<sub>2</sub>H, -Cl, -F, -Br, -I, -NO<sub>2</sub>, -CN, =O, -OH, -perfluoro C<sub>1-3</sub> alkyl, R<sub>5</sub>, -OR<sub>5</sub>, -NHR<sub>5</sub>, -OR<sub>9</sub>,  
 20 -N(R<sub>9</sub>)(R<sub>10</sub>), -R<sub>9</sub>, -C(O)-R<sub>10</sub>, and



25 provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub> group which comprises one or more additional -Ar<sub>3</sub> groups, said additional -Ar<sub>3</sub> groups are not substituted with another -Ar<sub>3</sub>.

30 Preferred compounds of this embodiment are those wherein:

m is 1;

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C is a ring chosen from the set consisting of benzo, pyrido, or thieno the ring optionally being singly or multiply substituted by halogen,  $-\text{NH}_2$ ,  $-\text{NH}-\text{R}_5$ ,  $-\text{NH}-\text{R}_9$ ,  $-\text{OR}_{10}$ , or  $-\text{R}_9$ , wherein  $\text{R}_9$  is a straight or branched  $\text{C}_{1-4}$  alkyl group and  $\text{R}_{10}$  is H or a straight or branched  $\text{C}_{1-4}$  alkyl group;

$\text{R}_6$  is H;

$\text{R}_{13}$  is H or a  $\text{C}_{1-4}$  straight or branched alkyl group optionally substituted with  $\text{Ar}_3$ ,  $-\text{OH}$ ,  $-\text{OR}_9$ ,  $-\text{CO}_2\text{H}$ , wherein the  $\text{R}_9$  is a  $\text{C}_{1-4}$  branched or straight chain alkyl group; wherein  $\text{Ar}_3$  is morpholinyl or phenyl, wherein the phenyl is optionally substituted with  $\text{Q}_1$ ;

$\text{R}_{21}$  is  $-\text{H}$  or  $-\text{CH}_3$ ;

$\text{R}_{51}$  is a  $\text{C}_{1-6}$  straight or branched alkyl group optionally substituted with  $\text{Ar}_3$ , wherein  $\text{Ar}_3$  is phenyl, optionally substituted by  $-\text{Q}_1$ ;

each  $\text{Ar}_3$  cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by  $-\text{Q}_1$ ;

each  $\text{Q}_1$  is independently selected from the group consisting of  $-\text{NH}_2$ ,  $-\text{Cl}$ ,  $-\text{F}$ ,  $-\text{Br}$ ,  $-\text{CH}_3$ ,  $-\text{R}_9$ ,  $-\text{NH}-\text{R}_5$  wherein  $\text{R}_5$  is  $-\text{C}(\text{O})-\text{R}_{10}$  or  $-\text{S}(\text{O})_2-\text{R}_9$ ,  $-\text{OR}_5$  wherein  $\text{R}_5$  is  $-\text{C}(\text{O})-\text{R}_{10}$ ,  $-\text{OR}_9$ ,  $-\text{NHR}_9$ , and

- 206 -

5

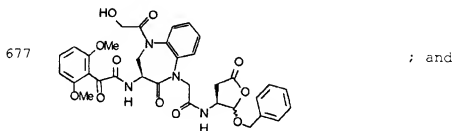


wherein each  $R_9$  and  $R_{10}$  are independently a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$  wherein  $Ar_3$  is phenyl;

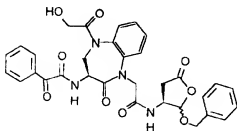
10 provided that when  $-Ar_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-Ar_3$  groups, said additional  $-Ar_3$  groups are not substituted with another  $-Ar_3$ .

15 Preferably, in this preferred embodiment,  $R_1$  is (w2) and the other substituents are as defined above.

Compounds of this preferred embodiment include, but are not limited to:



20 680



More preferably,  $R_8$  is selected from the

- 207 -

group consisting of:

- C(O)-R<sub>10</sub>,
- C(O)O-R<sub>9</sub>,
- C(O)-CH<sub>2</sub>-OR<sub>10</sub>, and
- C(O)-CH<sub>2</sub>C(O)-R<sub>9</sub>.

Most preferably, R<sub>8</sub> is -C(O)-CH<sub>2</sub>-OR<sub>10</sub> and R<sub>10</sub> is -H or -CH<sub>3</sub>.

Alternatively, in this preferred embodiment, R<sub>1</sub> is (e10) and X<sub>5</sub> is CH and the other substituents are as defined above.

Alternatively, in this preferred embodiment, R<sub>1</sub> is (e10) and X<sub>5</sub> is N and the other substituents are as defined above.

Preferably, in any of the above compounds of embodiment (K), R<sub>5</sub> is -C(O)-R<sub>10</sub> or -C(O)-C(O)-R<sub>10</sub> and the other substituents are as defined above.

More preferably, R<sub>10</sub> is -Ar<sub>3</sub> and the other substituents are as defined above.

More preferably, in these more preferred compounds:

R<sub>5</sub> is -C(O)-R<sub>10</sub> and R<sub>10</sub> is Ar<sub>3</sub>,

wherein the Ar<sub>3</sub> cyclic group is phenyl optionally being singly or multiply substituted by:

-R<sub>9</sub>, wherein R<sub>9</sub> is a C<sub>1-4</sub> straight or branched

alkyl group;

-F,

-Cl,

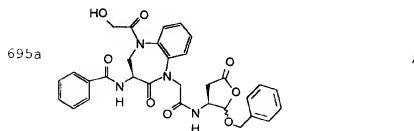
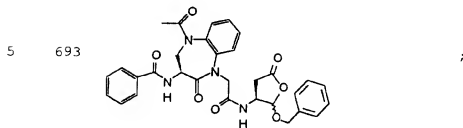
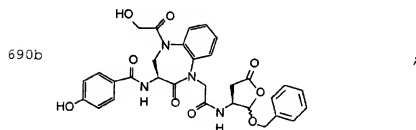
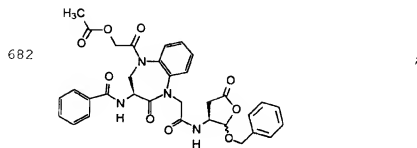
-N(H)-R<sub>5</sub>, wherein -R<sub>5</sub> is -H or -C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is a -C<sub>1-6</sub> straight or branched alkyl group

optionally substituted with Ar<sub>3</sub>, wherein Ar<sub>3</sub> is phenyl, -N(R<sub>9</sub>)(R<sub>10</sub>), wherein R<sub>9</sub> and R<sub>10</sub> are independently a -C<sub>1-4</sub> straight or branched alkyl group, or

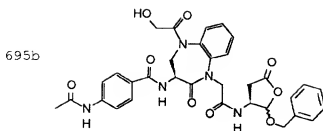
-O-R<sub>5</sub>, wherein R<sub>5</sub> is H or a -C<sub>1-4</sub> straight or branched alkyl group.

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Preferred compounds of this more preferred embodiment include, but are not limited to:

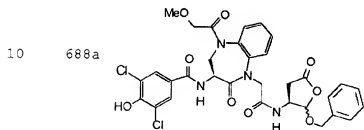
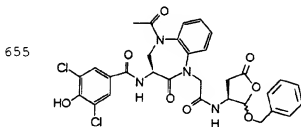


- 209 -

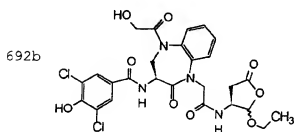
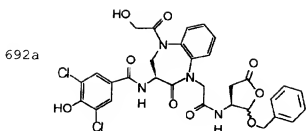


Most preferably,  $Ar_3$  is phenyl being singly or multiply substituted at the 3- or 5-position by -Cl or at the 4-position by -NH- $R_5$ ,  
 5 -N( $R_9$ )( $R_{10}$ ), or -O- $R_5$ .

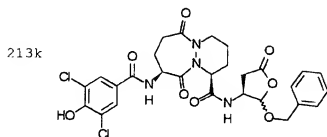
Preferred compounds of this most preferred embodiment include, but are not limited to:



- 210 -

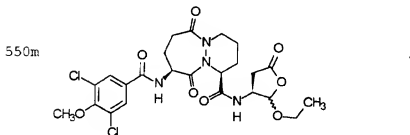
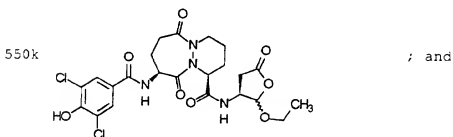
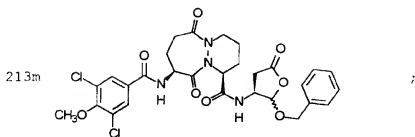


Other preferred compounds of  
this most preferred embodiment include, but are not  
5 limited to:





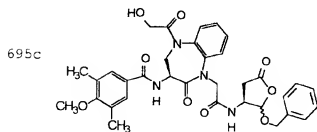
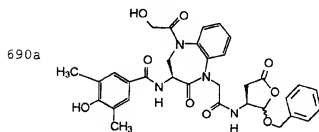
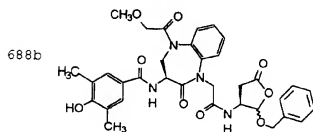
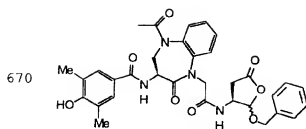
- 211 -



Alternatively, Ar<sub>3</sub> is phenyl being  
 5 singly or multiply substituted at the 3- or 5-position  
 by -R<sub>9</sub>, wherein R<sub>9</sub> is a C<sub>1-4</sub> straight or branched alkyl  
 group; and at the 4-position by -O-R<sub>5</sub>.

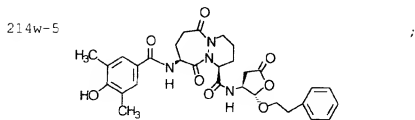
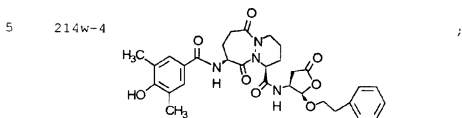
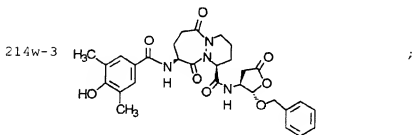
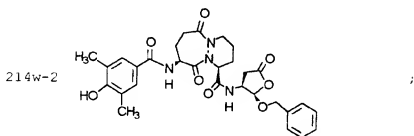
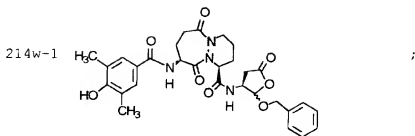
Preferred compounds of this  
 most preferred embodiment include, but are not limited  
 10 to:

- 212 -

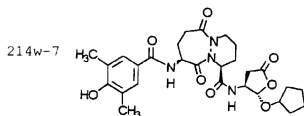
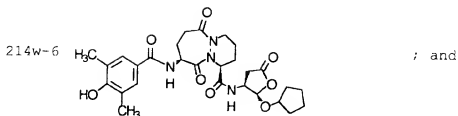


- 213 -

limited to:



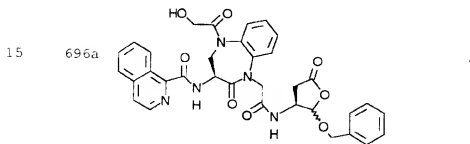
- 214 -



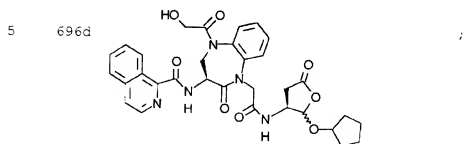
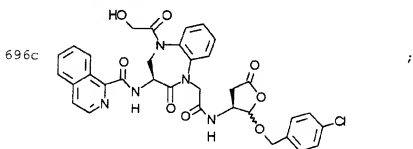
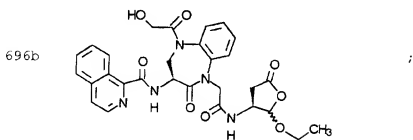
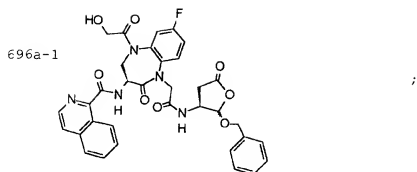
Alternatively, in this more preferred embodiment,  $R_5$  is  $-C(O)-R_{10}$ , wherein  $R_{10}$  is  $Ar_3$  and the  $Ar_3$  cyclic group is selected from the group consisting of is indolyl, benzimidazolyl, thienyl, quinolyl, isoquinolyl and benzo[b]thiophenyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ .

Most preferably, the  $Ar_3$  cyclic group is isoquinolyl.

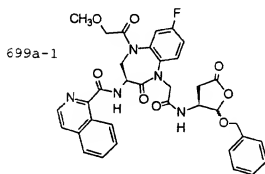
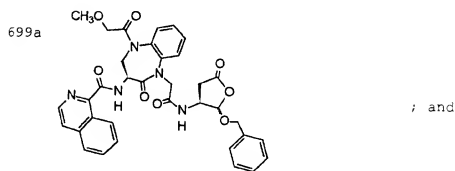
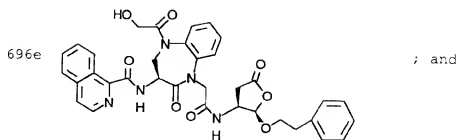
Preferred compounds of this most preferred embodiment include, but are not limited to:



- 215 -

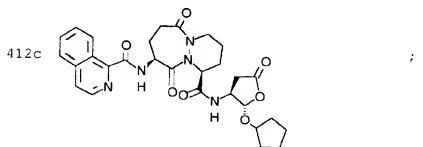
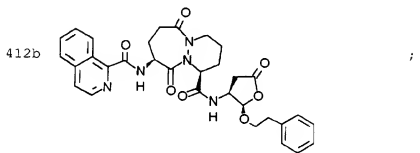
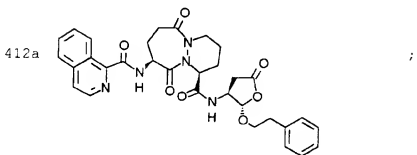
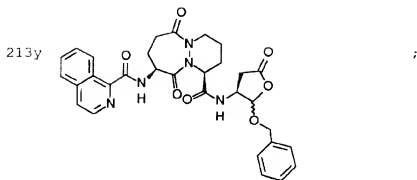


- 216 -

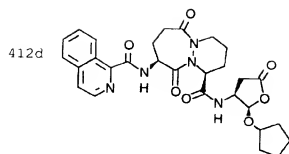


Other preferred compounds of this most preferred embodiment include, but are not limited to:

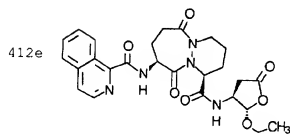
- 217 -



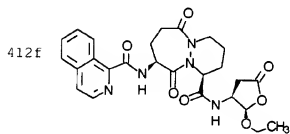
- 218 -



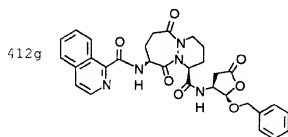
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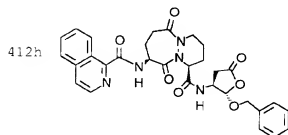


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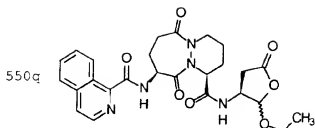
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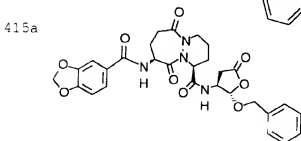
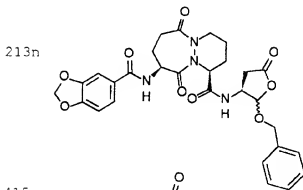
- 219 -



Alternatively, in this more preferred embodiment,  $R_5$  is  $-C(O)-R_{10}$ , wherein  $R_{10}$  is  $Ar_3$  and the  $Ar_3$  cyclic group is phenyl, substituted by

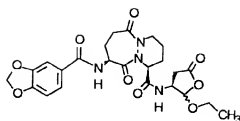


10 Preferred compounds of this more preferred embodiment include, but are not limited to:



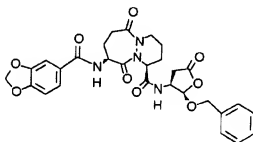
- 220 -

415b



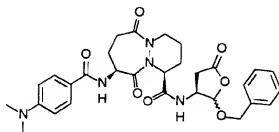
; and

415c



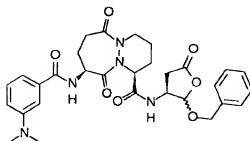
Other compounds of embodiment (K) include,  
5 but are not limited to:

213f



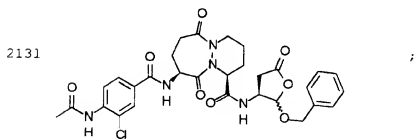
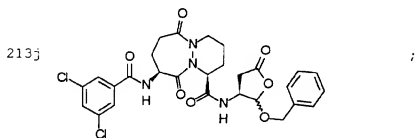
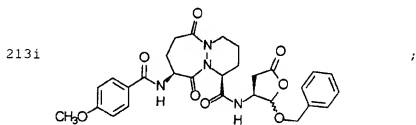
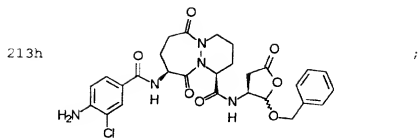
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213g

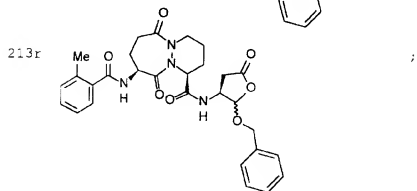
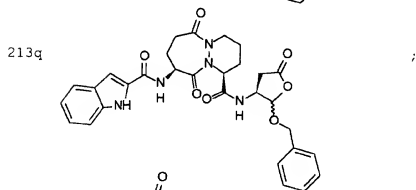
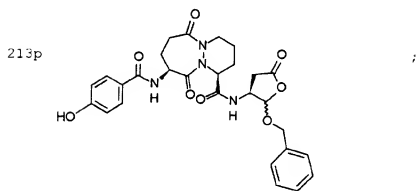
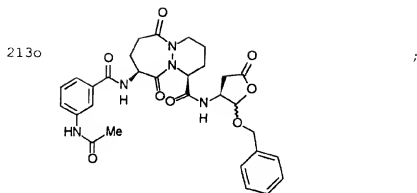


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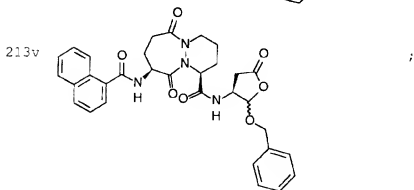
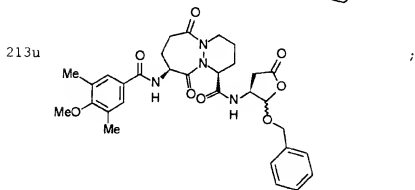
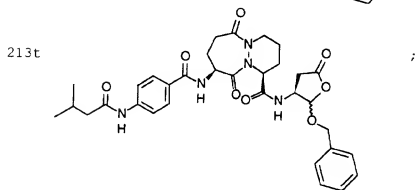
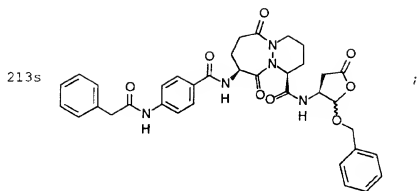
- 221 -



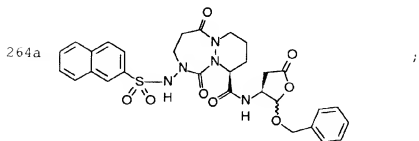
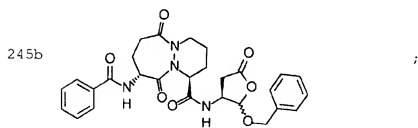
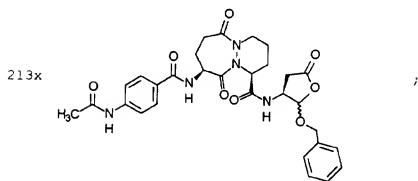
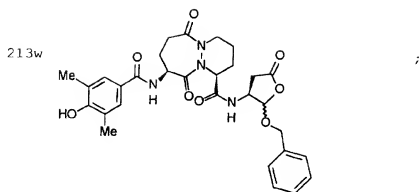
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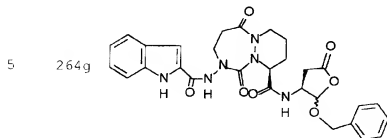
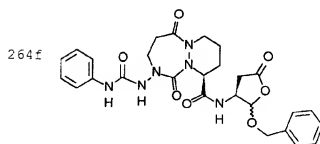
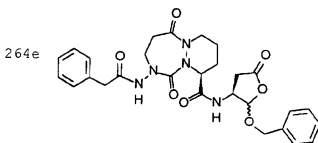
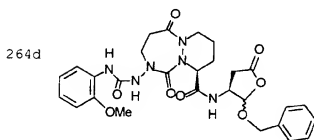
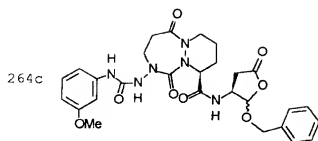
- 223 -



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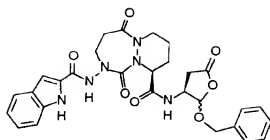


- 225 -

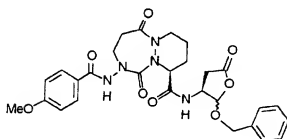


- 226 -

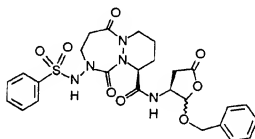
264h



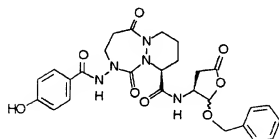
264i



264j

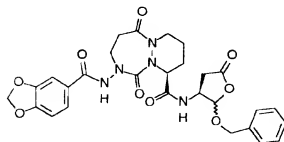


264k



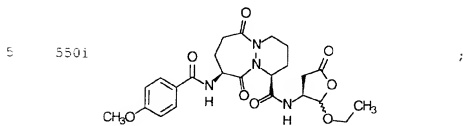
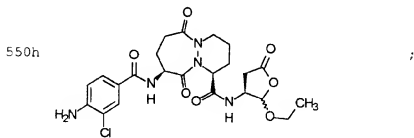
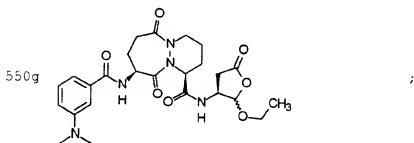
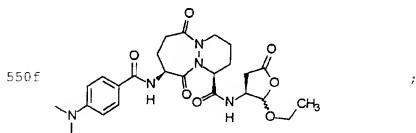
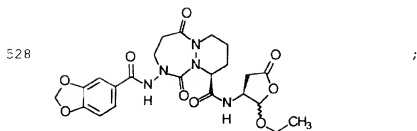
5

264l

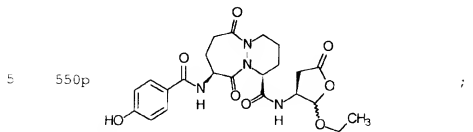
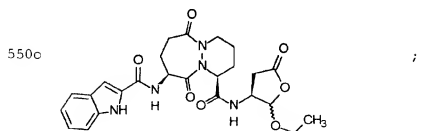
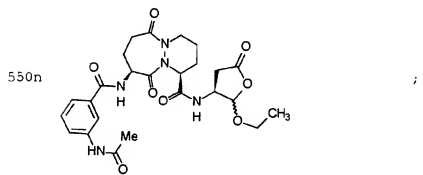
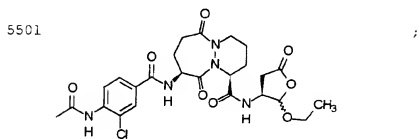
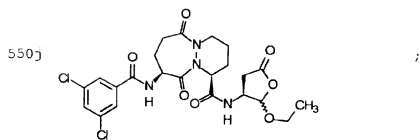




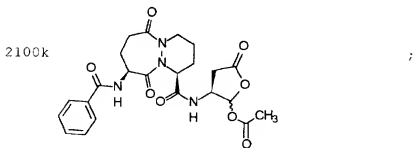
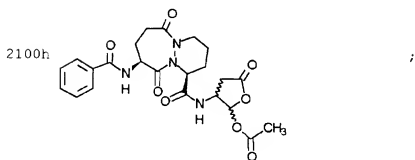
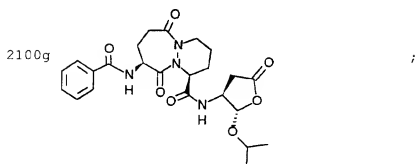
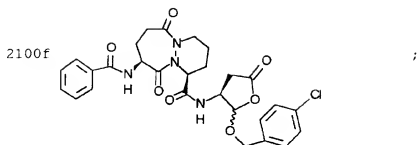
- 227 -



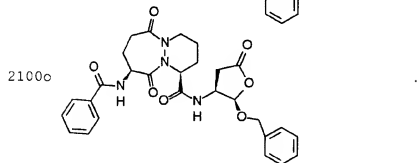
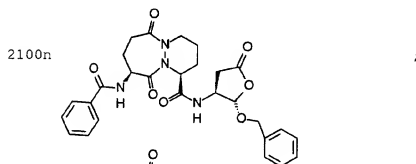
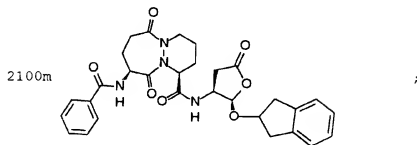
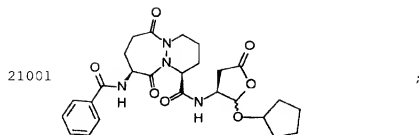
- 228 -



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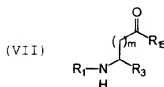
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5

The ICE inhibitors of another embodiment (L) of this invention are those of formula :

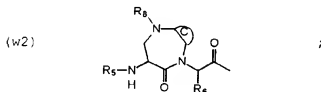
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wherein:

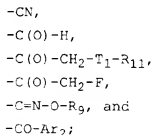
m is 1 or 2;

- 5             $\text{R}_1$  is selected from the group consisting of the following formulae:



- 10            C is a ring chosen from the set consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl, the ring optionally being singly or multiply substituted by  $-\text{Q}_1$ ;

- 15             $\text{R}_3$  is selected from the group consisting of:



each  $\text{R}_5$  is independently selected from the group consisting of:

- C(O)-R<sub>10</sub>,  
 25            -C(O)O-R<sub>9</sub>,

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5           -C(O)-N(R<sub>10</sub>)(R<sub>10</sub>)  
             -S(O)<sub>2</sub>-R<sub>9</sub>,  
             -S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
             -C(O)-CH<sub>2</sub>-O-R<sub>9</sub>,  
             -C(O)C(O)-R<sub>10</sub>,  
             -R<sub>9</sub>,  
             -H,  
             -C(O)C(O)-OR<sub>10</sub>, and  
             -C(O)C(O)-N(R<sub>9</sub>)(R<sub>10</sub>);

10

each T<sub>1</sub> is independently selected from the group  
consisting of -O-, -S-, -S(O)-, and -S(O)<sub>2</sub>-;

15           R<sub>6</sub> is selected from the group consisting of -H and  
             -CH<sub>3</sub>;

             R<sub>8</sub> is selected from the group consisting of:  
             -C(O)-R<sub>10</sub>,  
             -C(O)O-R<sub>9</sub>,  
             -C(O)-NH-R<sub>10</sub>,  
20           -S(O)<sub>2</sub>-R<sub>9</sub>,  
             -S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
             -C(O)-CH<sub>2</sub>-OR<sub>10</sub>,  
             -C(O)C(O)-R<sub>10</sub>,  
             -C(O)-CH<sub>2</sub>-N(R<sub>10</sub>)(R<sub>10</sub>),  
25           -C(O)-CH<sub>2</sub>C(O)-O-R<sub>9</sub>,  
             -C(O)-CH<sub>2</sub>C(O)-R<sub>9</sub>,  
             -H, and  
             -C(O)-C(O)-OR<sub>10</sub>;

30           each R<sub>9</sub> is independently selected from the group  
consisting of -Ar<sub>3</sub> and a -C<sub>1-6</sub> straight or branched  
alkyl group optionally substituted with Ar<sub>3</sub>, wherein  
the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

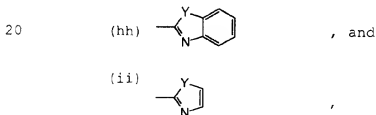
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each  $R_{10}$  is independently selected from the group consisting of -H,  $-Ar_3$ , a  $C_{3-6}$  cycloalkyl group, and a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$ , wherein the  $-C_{1-6}$  alkyl group is  
5 optionally unsaturated;

each  $R_{11}$  is independently selected from the group consisting of:  
- $Ar_4$ ,  
- $(CH_2)_{1-3}-Ar_4$ ,  
10 -H, and  
-C(O)- $Ar_4$ ;

$R_{15}$  is selected from the group consisting of -OH,  $-OAr_3$ ,  $-N(H)-OH$ , and  $-OC_{1-6}$ , wherein  $C_{1-6}$  is a straight or branched alkyl group optionally substituted with  
15  $Ar_3$ ,  $-CONH_2$ ,  $-OR_5$ ,  $-OH$ ,  $-OR_9$ , or  $-CO_2H$ ;

$Ar_2$  is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by  $-Q_1$  or phenyl, optionally substituted by  $Q_1$ :



wherein each Y is independently selected from the group consisting of O and S;

25 each  $Ar_3$  is a cyclic group independently selected from the set consisting of an aryl group which contains

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6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, and -NH-,  
 5 -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or  
 10 multiply substituted by -Q<sub>1</sub>;

each Ar<sub>4</sub> is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and  
 15 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, -NH-, -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally containing one or more double bonds, said heterocycle  
 20 group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Q<sub>1</sub> is independently selected from the group consisting of -NH<sub>2</sub>, -CO<sub>2</sub>H, -Cl, -F, -Br, -I, -NO<sub>2</sub>, -CN,  
 25 =O, -OH, -perfluoro C<sub>1-3</sub> alkyl, R<sub>5</sub>, -OR<sub>5</sub>, -NHR<sub>5</sub>, -OR<sub>9</sub>, -N(R<sub>9</sub>) (R<sub>10</sub>'), -R<sub>9</sub>, -C(O)-R<sub>10</sub>, and



30 provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub> group which comprises one or more additional -Ar<sub>3</sub>



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groups, said additional  $-Ar_3$  groups are not substituted with another  $-Ar_3$ .

Preferably,

m is 1;

5 C is a ring chosen from the set consisting of benzo, pyrido, and thieno, the ring optionally being singly or multiply substituted by halogen,  $-NH_2$ ,  $-NH-R_9$ , or  $-NH-R_9$ ,  $-OR_{10}$ , or  $-R_9$ , wherein  $R_9$  is a straight or branched  $-C_{1-4}$  alkyl group, and  $R_{10}$  is  $-H$  or  
10 a straight or branched  $-C_{1-4}$  alkyl group;

$T_1$  is O or S;

$R_6$  is H;

$R_{11}$  is selected from the group consisting of  $-Ar_4$ ,  
15  $-(CH_2)_{1-3}-Ar_4$ , and  $-C(O)-Ar_4$ ;

$Ar_2$  is (hh);

Y is O;

each  $Ar_3$  cyclic group is independently selected  
20 from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, thiazolyl, benzimidazolyl, thienothienyl, thiadiazolyl, benzotriazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply  
25 substituted by  $-Q_1$ ;

each  $Ar_4$  cyclic group is independently selected from the set consisting of phenyl, tetrazolyl,

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naphthyl, pyridinyl, oxazolyl, pyrimidinyl, or indolyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

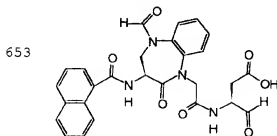
each  $Q_1$  is independently selected from the group consisting of  $-\text{NH}_2$ ,  $-\text{Cl}$ ,  $-\text{F}$ ,  $-\text{Br}$ ,  $-\text{OH}$ ,  $-\text{R}_9$ ,  $-\text{NH}-\text{R}_5$  wherein  $\text{R}_5$  is  $-\text{C}(\text{O})-\text{R}_{10}$  or  $-\text{S}(\text{O})_2-\text{R}_9$ ,  $-\text{OR}_5$  wherein  $\text{R}_5$  is  $-\text{C}(\text{O})-\text{R}_{10}$ ,  $-\text{OR}_9$ ,  $-\text{NHR}_9$ , and



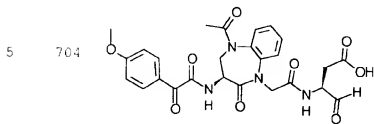
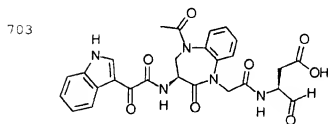
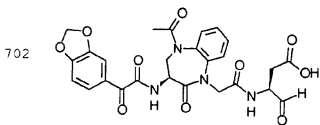
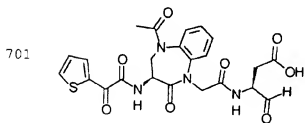
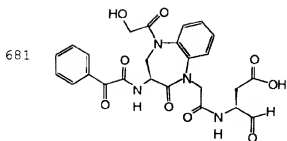
wherein each  $\text{R}_9$  and  $\text{R}_{10}$  are independently a  $-\text{C}_{1-6}$  straight or branched alkyl group optionally substituted with  $-\text{Ar}_3$  wherein  $\text{Ar}_3$  is phenyl;

provided that when  $-\text{Ar}_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-\text{Ar}_3$  groups, said additional  $-\text{Ar}_3$  groups are not substituted with another  $-\text{Ar}_3$ .

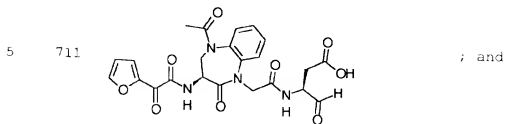
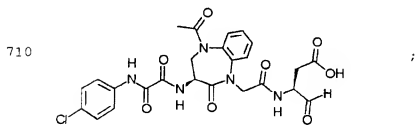
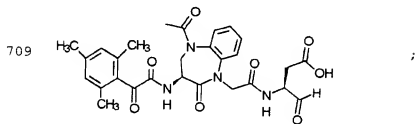
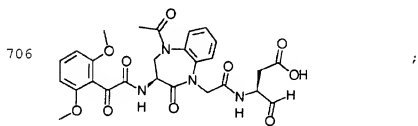
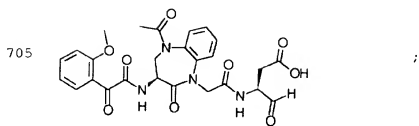
Preferred compounds of this preferred embodiment include, but are not limited to:



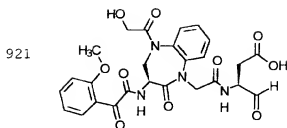
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More preferably,  $R_3$  is  $-C(O)-Ar_2$   
and the other substituents are as described above.

Alternatively,  $R_3$  is

5  $-C(O)CH_2-T_1-R_{11}$ ;

Alternatively,  $R_3$  is  $-C(O)-H$ .

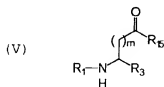
Preferably, in any of the above compounds of  
embodiment (L),  $R_8$  is selected from the group  
consisting of:

10  $-C(O)-R_{10}$ ,  
 $-C(O)O-R_9$ ,  
 $-C(O)-CH_2-OR_{10}$ , and  
 $-C(O)-CH_2C(O)-R_9$ .

More preferably,  $R_8$  is  $-C(O)-CH_2-OR_{10}$  and

15  $R_{10}$  is  $-H$  or  $-CH_3$ .

Alternatively, ICE inhibitors of embodiment  
(L) of this invention are those of formula :

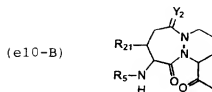


wherein:

20  $m$  is 1;

$R_1$  is:

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$R_3$  is selected from the group consisting of:

- CN,
- C(O)-H,
- C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>,
- C(O)-CH<sub>2</sub>-F,
- C=N-O-R<sub>9</sub>, and
- CO-Ar<sub>2</sub>;

each  $R_5$  is independently selected from the group consisting of:

- C(O)-R<sub>10</sub>,
- C(O)O-R<sub>9</sub>,
- C(O)-N(R<sub>10</sub>)(R<sub>10</sub>)
- S(O)<sub>2</sub>-R<sub>9</sub>,
- S(O)<sub>2</sub>-NH-R<sub>10</sub>,
- C(O)-CH<sub>2</sub>-O-R<sub>9</sub>,
- C(O)C(O)-R<sub>10</sub>,
- R<sub>9</sub>,
- H,
- C(O)C(O)-OR<sub>10</sub>, and
- C(O)C(O)-N(R<sub>9</sub>)(R<sub>10</sub>);

$Y_2$  is H<sub>2</sub> or O;

each  $T_1$  is independently selected from the group consisting of -O- or -S-;

each  $R_9$  is independently selected from the group

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consisting of  $-Ar_3$  and a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$ , wherein the  $-C_{1-6}$  alkyl group is optionally unsaturated;

5 each  $R_{10}$  is independently selected from the group consisting of  $-H$ ,  $-Ar_3$ , a  $C_{3-6}$  cycloalkyl group, and a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$ , wherein the  $-C_{1-6}$  alkyl group is optionally unsaturated;

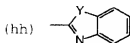
10 each  $R_{11}$  is independently selected from the group consisting of:

$-Ar_4$ ,  
 $-(CH_2)_{1-3}-Ar_4$ ,  
 $-H$ , and  
 $-C(O)-Ar_4$ ;

15  $R_{15}$  is selected from the group consisting of  $-OH$ ,  $-OAr_3$ ,  $-N(H)-OH$ , and  $-OC_{1-6}$ , wherein  $C_{1-6}$  is a straight or branched alkyl group optionally substituted with  $-Ar_3$ ,  $-CONH_2$ ,  $-OR_5$ ,  $-OH$ ,  $-OR_9$ , or  $-CO_2H$ ;

$R_{21}$  is  $-H$  or  $-CH_3$ ;

20  $Ar_2$  is:



wherein  $Y$  is  $O$ ;

25 each  $Ar_3$  is a cyclic group independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl,

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isoxazolyl, benzotriazolyl, benzimidazolyl,  
 thienothieryl, imidazolyl, thiadiazolyl,  
 benzo[b]thiophenyl, pyridyl benzofuranyl, and indolyl,  
 and said cyclic group optionally being singly or  
 5 multiply substituted by  $-Q_1$ ;

each  $Ar_4$  is a cyclic group independently selected  
 from the set consisting of phenyl, tetrazolyl,  
 pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and  
 thienyl, and said cyclic group optionally being singly  
 10 or multiply substituted by  $-Q_1$ ;

each  $Q_1$  is independently selected from the group  
 consisting of  $-NH_2$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-OH$ ,  $-R_9$ ,  $-NH-R_5$   
 wherein  $R_5$  is  $-C(O)-R_{10}$  or  $-S(O)_2-R_9$ ,  $-OR_5$  wherein  $R_5$  is  
 $-C(O)-R_{10}$ ,  $-OR_9$ ,  $-NHR_9$ , and



20 provided that when  $-Ar_3$  is substituted with a  $Q_1$   
 group which comprises one or more additional  $-Ar_3$   
 groups, said additional  $-Ar_3$  groups are not substituted  
 with another  $-Ar_3$ ;

provided that when:

25  $m$  is 1;  
 $R_{15}$  is  $-OH$ ;  
 $R_{21}$  is  $-H$ ; and

$Y_2$  is  $O$  and  $R_3$  is  $-C(O)-H$ , then  $R_5$  cannot be:  
 $-C(O)-R_{10}$ , wherein  $R_{10}$  is  $-Ar_3$  and the  $Ar_3$  cyclic



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group is phenyl, unsubstituted by  $-Q_1$ , 4-(carboxymethoxy)phenyl, 2-fluorophenyl, 2-pyridyl, N-(4-methylpiperazino)methylphenyl, or

$-C(O)-OR_9$ , wherein  $R_9$  is  $-CH_2-Ar_3$ , and the  $Ar_3$  cyclic group is phenyl, unsubstituted by  $-Q_1$ ; and when

$Y_2$  is O,  $R_3$  is  $-C(O)-CH_2-T_1-R_{11}$ ,  $T_1$  is O, and  $R_{11}$  is  $Ar_4$ , wherein the  $Ar_4$  cyclic group is 5-(1-(4-chlorophenyl)-3-trifluoromethyl)pyrazolyl), then  $R_5$  cannot be:

-H;

$-C(O)-R_{10}$ , wherein  $R_{10}$  is  $-Ar_3$  and the  $Ar_3$  cyclic group is 4-(dimethylaminomethyl)phenyl, phenyl, 4-(carboxymethylthio)phenyl, 4-(carboxyethylthio)phenyl, 4-(carboxyethyl)phenyl, 4-(carboxypropyl)phenyl, 2-fluorophenyl, 2-pyridyl, N-(4-methylpiperazino)methylphenyl, or

$-C(O)-OR_9$ , wherein  $R_9$  is isobutyl or  $-CH_2-Ar_3$  and the  $Ar_3$  cyclic group is phenyl;

and when  $R_{11}$  is  $Ar_4$ , wherein the  $Ar_4$  cyclic group is 5-(1-phenyl-3-trifluoromethyl)pyrazolyl or 5-(1-(4-chloro-2-pyridinyl)-3-trifluoromethyl)pyrazolyl, then  $R_5$  cannot be:

$-C(O)-OR_9$ , wherein  $R_9$  is  $-CH_2-Ar_3$ , and the  $Ar_3$  cyclic group is phenyl;

and when  $R_{11}$  is  $Ar_4$ , wherein the  $Ar_4$  cyclic group is 5-(1-(2-pyridyl)-3-trifluoromethyl)pyrazolyl), then  $R_5$  cannot be:

$-C(O)-R_{10}$ , wherein  $R_{10}$  is  $-Ar_3$  and the  $Ar_3$  cyclic group is 4-(dimethylaminomethyl)phenyl, or

$-C(O)-OR_9$ , wherein  $R_9$  is  $-CH_2-Ar_3$ , and the  $Ar_3$  cyclic group is phenyl, unsubstituted by  $-Q_1$ ; and when

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$Y_2$  is O,  $R_3$  is  $-C(O)-CH_2-T_1-R_{11}$ ,  $T_1$  is O, and  $R_{11}$  is  $-C(O)-Ar_4$ , wherein the  $Ar_4$  cyclic group is 2,5-dichlorophenyl, then  $R_5$  cannot be:

-C(O)- $R_{10}$ , wherein  $R_{10}$  is  $-Ar_3$  and the  $Ar_3$  cyclic group is 4-(dimethylaminomethyl)phenyl, 4-(N-morpholinomethyl)phenyl, 4-(N-methylpiperazinomethyl)phenyl, 4-(N-(2-methylimidazolylmethyl)phenyl, 5-benzimidazolyl, 5-benzotriazolyl, N-carboethoxy-5-benzotriazolyl, N-carboethoxy-5-benzimidazolyl, or

-C(O)-OR<sub>9</sub>, wherein  $R_9$  is  $-CH_2-Ar_3$ , and the  $Ar_3$  cyclic group is phenyl, unsubstituted by  $-Q_1$ ; and when

$Y_2$  is  $H_2$ ,  $R_3$  is  $-C(O)-CH_2-T_1-R_{11}$ ,  $T_1$  is O, and  $R_{11}$  is  $-C(O)-Ar_4$ , wherein the  $Ar_4$  cyclic group is 2,5-dichlorophenyl, then  $R_5$  cannot be:

-C(O)-OR<sub>9</sub>, wherein  $R_9$  is  $-CH_2-Ar_3$  and the  $Ar_3$  cyclic group is phenyl.

Preferably, in any of the above compounds of embodiment (L),  $R_3$  is  $-C(O)-H$  and  $R_5$  is  $-C(O)-R_{10}$  or  $-C(O)-C(O)-R_{10}$  and the other substituents are as defined above.

More preferably  $R_{10}$  is  $-Ar_3$  and the other substituents are as defined above.

More preferably in these more preferred compounds:

$R_5$  is  $-C(O)-R_{10}$  and  $R_{10}$  is  $Ar_3$ , wherein the  $Ar_3$  cyclic group is phenyl optionally being singly or multiply substituted by:

- $R_9$ , wherein  $R_9$  is a  $C_{1-4}$  straight or branched alkyl group;

-F,

-Cl,

-N(H)- $R_5$ , wherein  $-R_5$  is  $-H$  or  $-C(O)-R_{10}$ ,

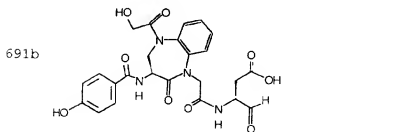
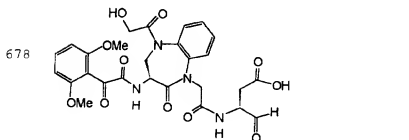
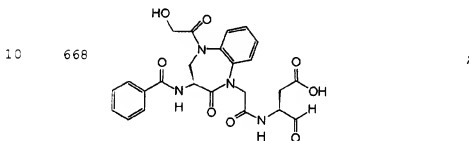
- 245 -

wherein  $R_{10}$  is a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$ , wherein  $Ar_3$  is phenyl,

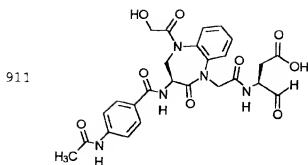
5  $-N(R_9)(R_{10})$ , wherein  $R_9$  and  $R_{10}$  are independently a  $-C_{1-4}$  straight or branched alkyl group, or

$-O-R_5$ , wherein  $R_5$  is H or a  $-C_{1-4}$  straight or branched alkyl group.

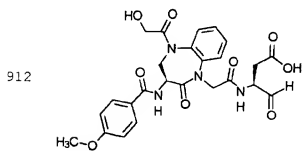
Preferred compounds of this preferred embodiment include, but are not limited to:



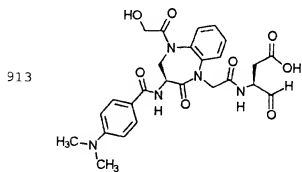
- 246 -



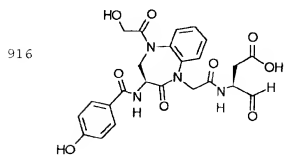
;



;



; and

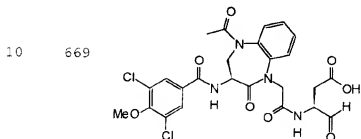
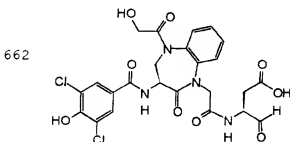
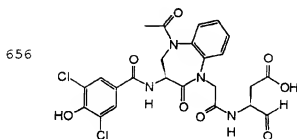


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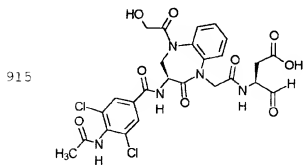
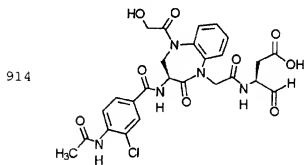
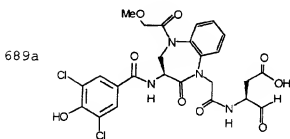
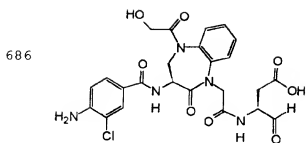
- 247 -

Most preferably, Ar<sub>3</sub> is phenyl being singly or multiply substituted at the 3- or 5-position by -Cl or at the 4-position by -NH-R<sub>5</sub>, -N(R<sub>9</sub>) (R<sub>10</sub>), or -O-R<sub>5</sub>.

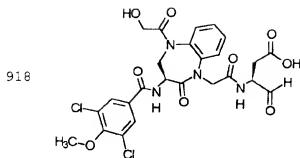
5 Preferred compounds of this most preferred embodiment include, but are not limited to:



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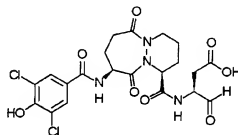
- 249 -



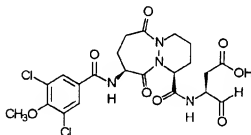
Other preferred compounds of this most preferred embodiment include, but are not limited to:

5      214k

; and



214m



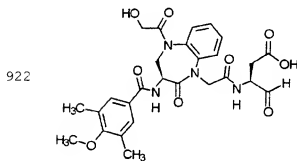
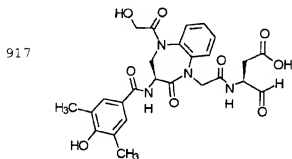
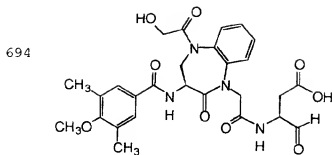
Alternatively, Ar<sub>3</sub> is phenyl being singly or multiply substituted at the 3- or 5-position by -R<sub>9</sub>, wherein R<sub>9</sub> is a C<sub>1-4</sub> straight or branched alkyl group; and at the 4-position by -O-R<sub>5</sub>.

Preferred compounds of this most preferred embodiment include, but are not limited to:

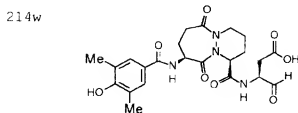




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Another preferred compound of  
 5 this most preferred embodiment includes, but is not  
 limited to:

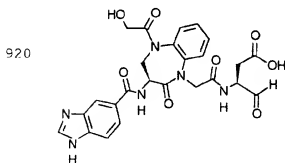
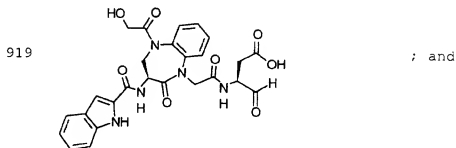


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Alternatively, in this more preferred embodiment:

R<sub>5</sub> is -C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is Ar<sub>3</sub> and the Ar<sub>3</sub> cyclic group is selected from the group consisting of indolyl, benzimidazolyl, thienyl, quinolyl, isoquinolyl and benzo[b]thiophenyl, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>.

Preferred compounds of this more  
10 preferred embodiment include, but are not limited to:



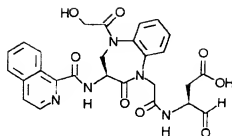
Most preferably, the Ar<sub>3</sub> cyclic group is isoquinolyl, and said cyclic group optionally 15 being singly or multiply substituted by -Q<sub>1</sub>.

A preferred compound of this most preferred embodiment includes, but is not limited:

- 253 -

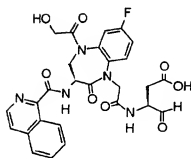
to:

696



;

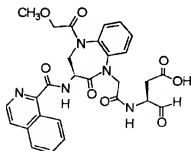
696-1



; and

5

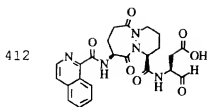
699



.

Another preferred compound of this most preferred embodiment includes, but is not limited to:

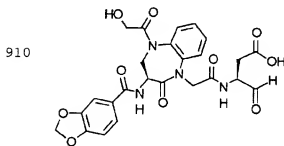
- 254 -



Alternatively, in this more preferred  
embodiment  $R_5$  is  $-C(O)-R_{10}$ , wherein  $R_{10}$  is  $-Ar_3$  and the  
5  $Ar_3$  cyclic group is phenyl, substituted by

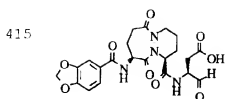


A preferred compound of this more  
preferred embodiment includes, but is not limited to:

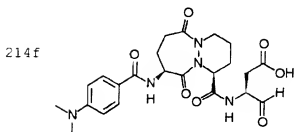


15 A preferred compound of this more  
preferred embodiment includes, but is not limited to:

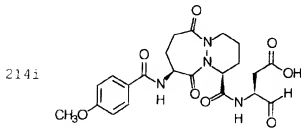
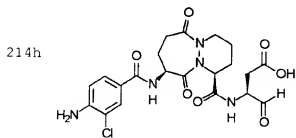
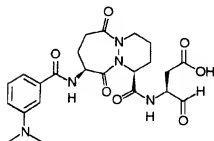
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Other compounds of embodiment (L) include,  
but are not limited to:

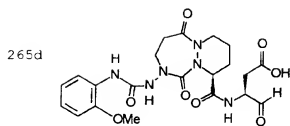


5 214g

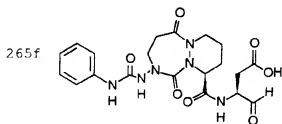




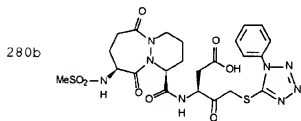
- 257 -



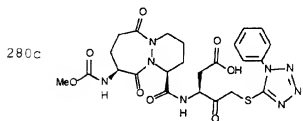
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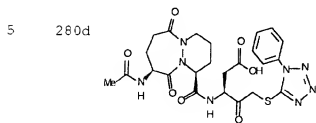
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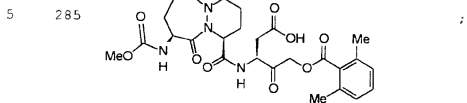
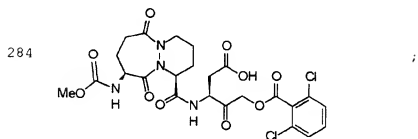
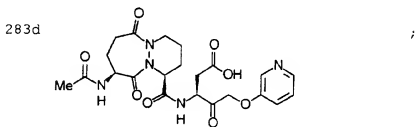
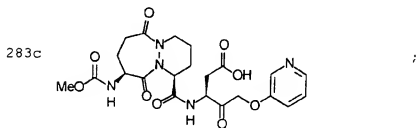
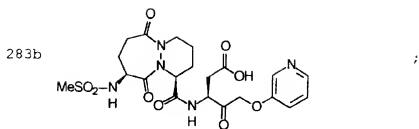


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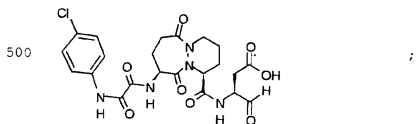
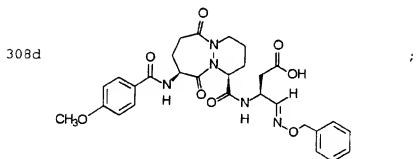
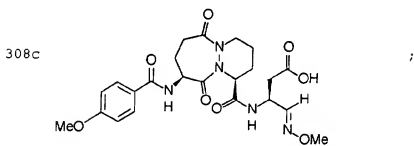
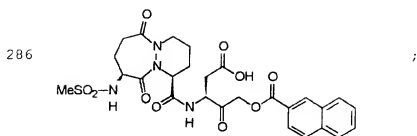
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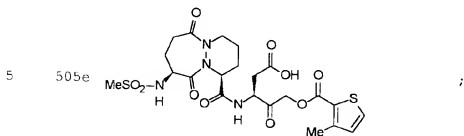
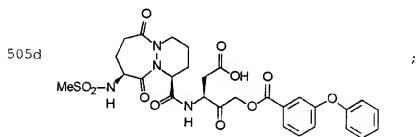
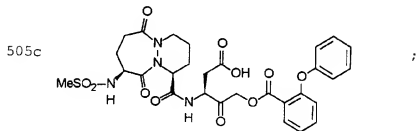
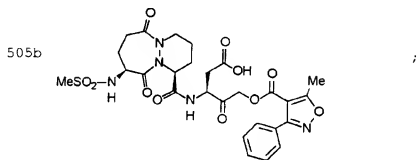
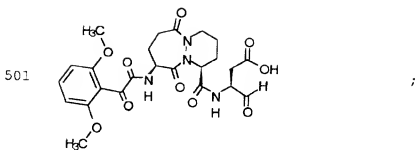




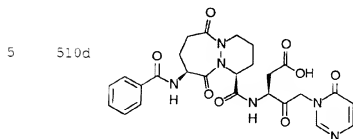
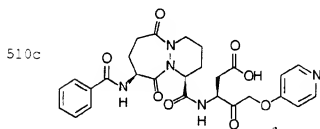
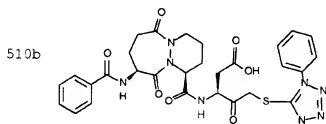
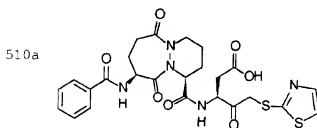
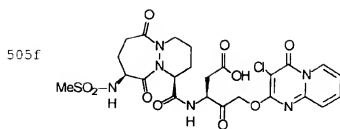
- 259 -



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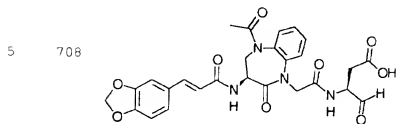
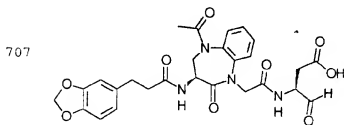
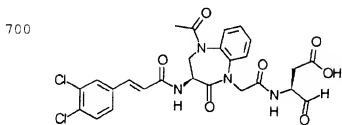
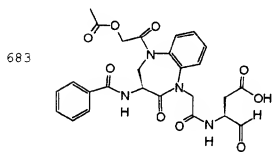
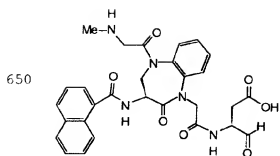


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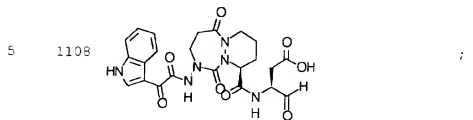
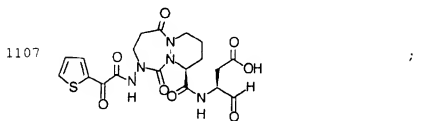
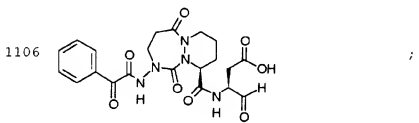
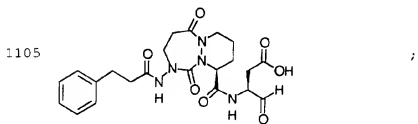
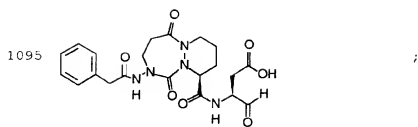


- 263 -





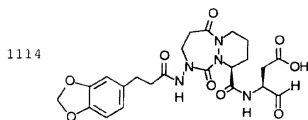
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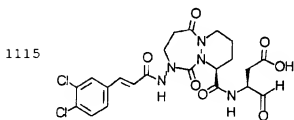




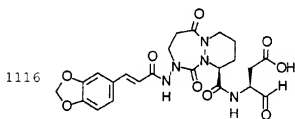
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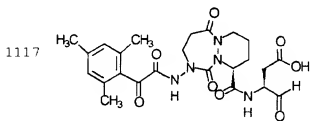
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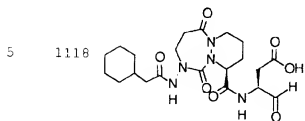
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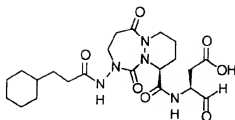
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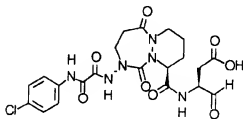
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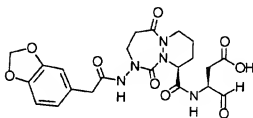
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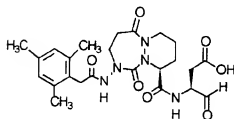
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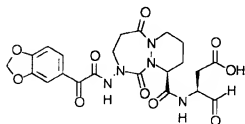
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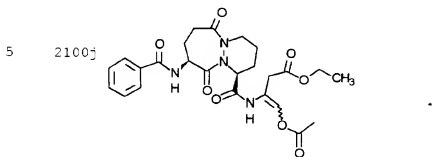
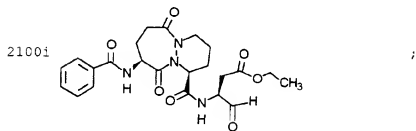
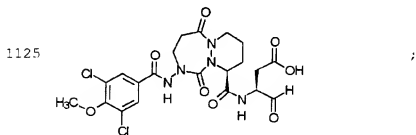
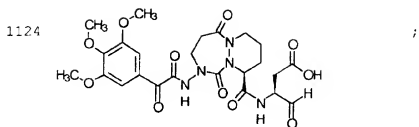
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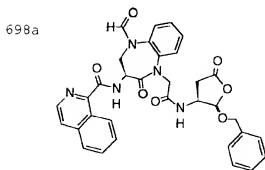
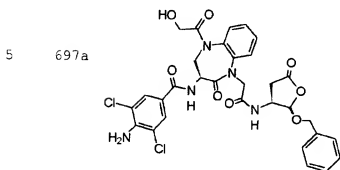
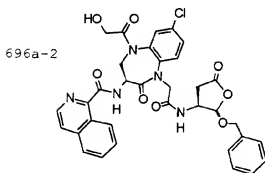
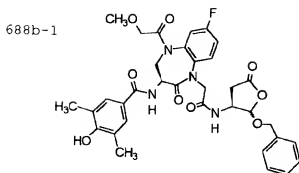
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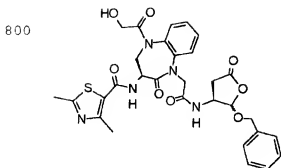


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but are not limited to:

- 270 -



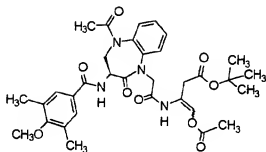
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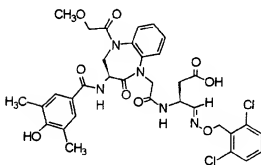
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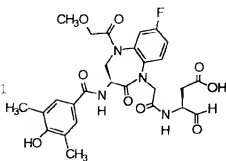
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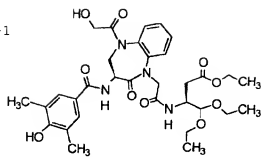
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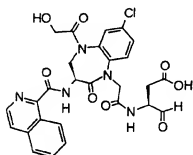
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- 272 -

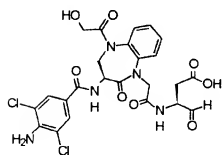
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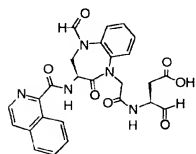
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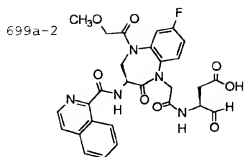
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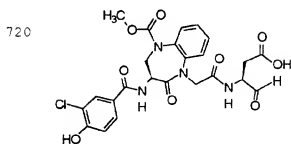
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- 273 -

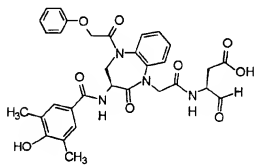


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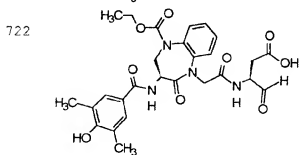


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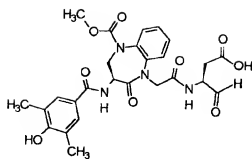
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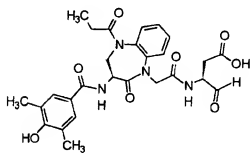
- 274 -

723



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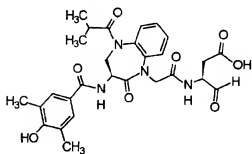
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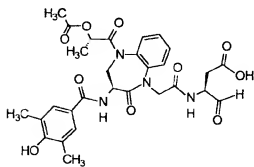
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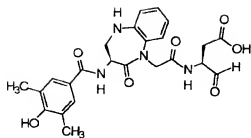
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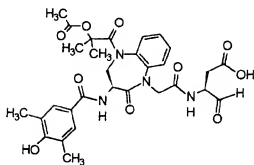


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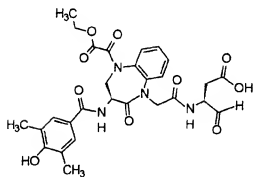


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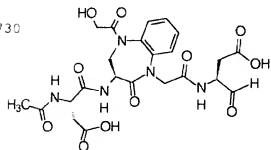


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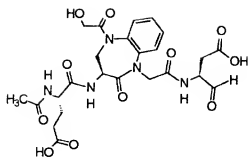


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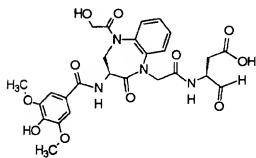
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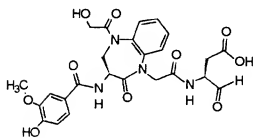
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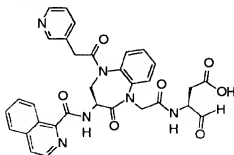
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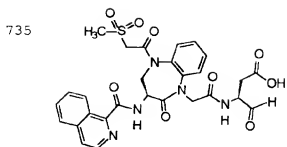
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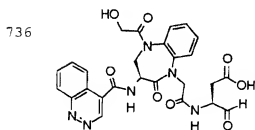


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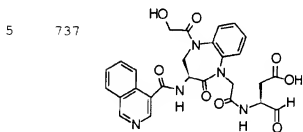
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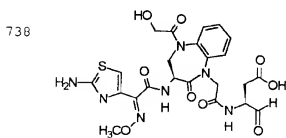
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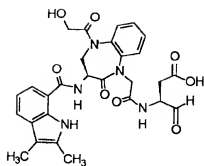
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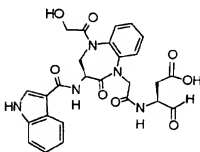
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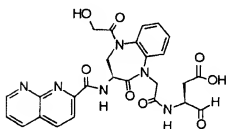
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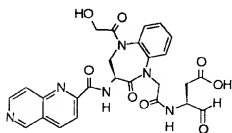
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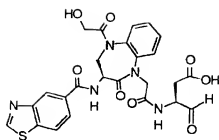
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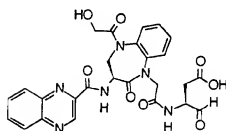
- 279 -

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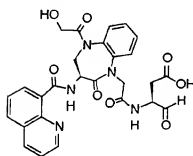
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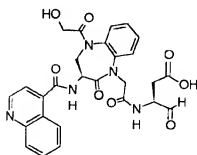
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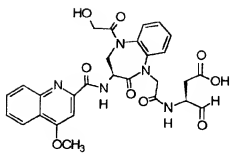
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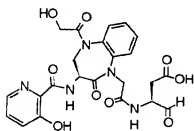
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- 280 -

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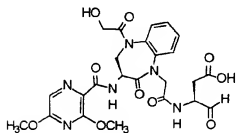


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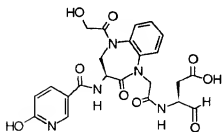


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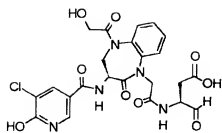


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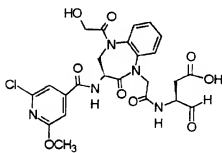
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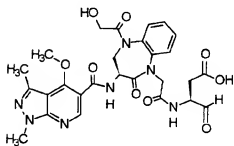
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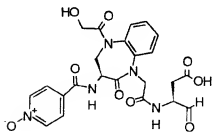
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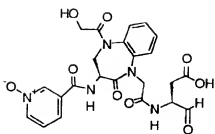
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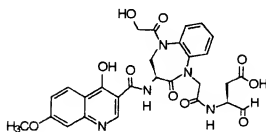
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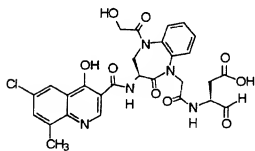
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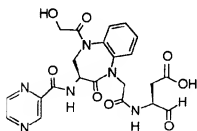
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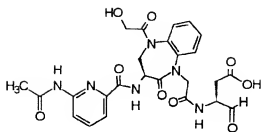


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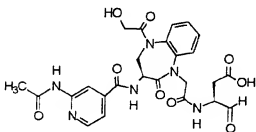
- 283 -

759



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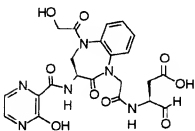
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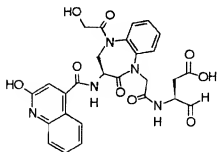
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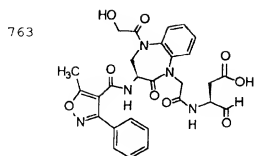
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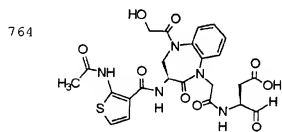


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- 284 -

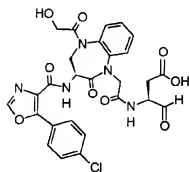


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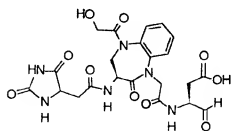
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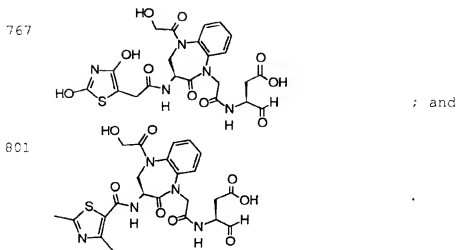
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The most preferred compounds of embodiments (K) and (L) are those wherein the Ar<sub>3</sub> cyclic group is isoquinolyl.

Compounds of this invention are described in co-pending United States Application Serial Nos. 08/575,641 and 08/598,332 the disclosures of which are herein incorporated by reference.

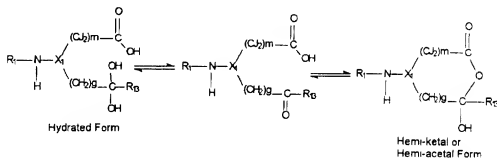
The compounds of this invention have a molecular weight of less than or equal to about 700 Daltons, and more preferably between about 400 and 600 Daltons. These preferred compounds may be readily absorbed by the bloodstream of patients upon oral administration. This oral availability makes such compounds excellent agents for orally-administered treatment and prevention regimens against IL-1-, apoptosis-, IGIF- or IFN- $\gamma$  mediated diseases.

It should be understood that the compounds of this invention may exist in various equilibrium forms, depending on conditions including choice of solvent, pH, and others known to the practitioner skilled in the art. All such forms of these compounds are expressly included in the present invention. In particular, many

- 286 -

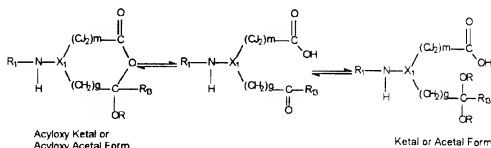
of the compounds of this invention, especially those which contain aldehyde or ketone groups in  $R_3$  and carboxylic acid groups in T, may take hemi-ketal (or hemi-acetal) or hydrated forms. For example, compounds of embodiment (A) may take the forms depicted below:

5 EQ1



Depending on the choice of solvent and other conditions known to the practitioner skilled in the art, compounds of this invention may also take acyloxy ketal, acyloxy acetal, ketal or acetal form:

10



In addition, it should be understood that the equilibrium forms of the compounds of this invention may include tautomeric forms. All such forms of these compounds are expressly included in the present invention.

15

It should be understood that the compounds of this invention may be modified by appropriate

- 287 -

functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion. In addition, the compounds may be altered to pro-drug form such that the desired compound is created in the body of the patient as the result of the action of metabolic or other biochemical processes on the pro-drug. Such pro-drug forms typically demonstrate little or no activity in *in vitro* assays. Some examples of pro-drug forms include ketal, acetal, oxime, imine, and hydrazone forms of compounds which contain ketone or aldehyde groups, especially where they occur in the R<sub>3</sub> group of the compounds of this invention. Other examples of pro-drug forms include the hemi-ketal, hemi-acetal, acyloxy ketal, acyloxy acetal, ketal, and acetal forms that are described in EQ1 and EQ2.

#### ICE and TX Cleave and Thereby Activate Pro-IGIF

The ICE protease was identified previously by virtue of its ability to process inactive pro-IL-1 $\beta$  to mature active IL-1 $\beta$ , a pro-inflammatory molecule, in vitro and in vivo. Here we show that ICE and its close homologue TX (Caspase-4, C. Faucheu et al., EMBO, 14, p. 1914 (1995)) can proteolytically cleave inactive pro-IGIF. This processing step is required to convert pro-IGIF to its active mature form, IGIF. Cleavage of pro-IGIF by ICE, and presumably by TX, also facilitates the export of IGIF out of cells.

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We first used transient co-expression of plasmids transfected into Cos cells to determine whether any known members of the ICE/CED-3 protease family can process pro-IGIF to IGIF in cultured cells (Example 23) (Fig. 1A).

Fig. 1A demonstrates that ICE cleaves pro-IGIF in Cos cells co-transfected with plasmids that express pro-IGIF in the presence of active ICE. Cos cells were transfected with an expression plasmid for pro-IGIF alone (lane 2) or in combination with the indicated expression plasmids encoding wild type or inactive mutants of ICE/CED-3 family of proteases (lanes 3-12). Cell lysates were prepared and analyzed for the presence of IGIF protein by immunoblotting with an anti-IGIF antiserum. Lane 1 contained lysates from mock transfected cells.

Co-expression of pro-IGIF with ICE or TX resulted in the cleavage of pro-IGIF into a polypeptide similar in size to the naturally-occurring 18-kDa mature IGIF. This processing event is blocked by single point mutations that alter the catalytic cysteine residues and thus inactivate ICE and TX (Y. Gu et al., EMBO, 14, p. 1923 (1995)).

Co-expression with CPP32 (Caspase-3), a protease involved in programmed cell death (T. Fernandes-Alnemri et al., J. Biol. Chem., 269, p. 30761 (1994); D. W. Nicholson et al., Nature, 376, p. 37 (1995)), resulted in the cleavage of pro-IGIF into a smaller polypeptide, while co-expression with CMH-1 (Caspase-7), a close homolog of CPP32 (J. A. Lippke et al., J. Biol. Chem., 271, p. 1825 (1996)), failed to cleave pro-IGIF to any significant extent. Thus, ICE and TX appear to be capable of cleaving pro-IGIF into a

- 289 -

polypeptide similar in size to the naturally-occurring 18-kDa IGIF.

We next examined the ability of these cysteine proteases to cleave pro-IGIF in vitro using a purified, recombinant (His)<sub>6</sub>-tagged pro-IGIF as a substrate (Example 23).

Fig. 1B demonstrates that pro-IGIF is cleaved in vitro by ICE. Purified recombinant (His)<sub>6</sub>-tagged pro-IGIF (2 µg) was incubated with the indicated cysteine protease in the presence or absence of ICE or CPP32 inhibitors as described in Example 23. The cleavage products were analyzed by SDS-PAGE and Coomassie Blue staining.

ICE cleaved the 24 kDa pro-IGIF into two polypeptides of approximately 18-kDa and 6-kDa. N-terminal amino acid sequencing of the ICE cleavage products indicated that the 18-kDa polypeptide contains the same N-terminal amino acid residues (Asn-Phe-Gly-Arg-Leu) as the naturally occurring IGIF. This shows that ICE cleaves pro-IGIF at the authentic processing site (Asp35-Asn36) (H. Okamura et al., Infection and Immunity, 63, p. 3966 (1995); H. Okamura et al., Nature, 378, p. 88 (1995)). N-terminal amino acid sequencing of the CPP32 cleavage products indicated that CPP32 cleaved pro-IGIF at Asp69-Ile70.

The cleavage by ICE of pro-IGIF is highly specific with a catalytic efficiency ( $k_{cat}/K_M$ ) of  $1.4 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$  ( $K_M = 0.6 \pm 0.1 \text{ µM}$ ;  $k_{cat} = 8.6 \pm 0.3 \text{ s}^{-1}$ ) and is inhibited by specific ICE inhibitors (Ac-Tyr-Val-Ala-Asp-aldehyde) and Cbz-Val-Ala-Asp-[(2,6-dichlorobenzoyl)oxyl)methylketone, (N.A. Thornberry et al., Nature, 356, p. 768 (1992); R. E. Doile et al., J. Med. Chem., 37, p. 563 (1994)).

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Fig. 1C demonstrates that ICE cleavage in vitro activates pro-IGIF. Uncleaved pro-IGIF, ICE- or CPP32-cleaved products of pro-IGIF, or recombinant mature IGIF (rIGIF) were each added to A.E7 cell  
5 cultures to a final concentration of 12 ng/ml or 120 ng/ml (see, **Example 23**). Eighteen hours later, IFN- $\gamma$  in the cultural medium was quantified by ELISA. While the uncleaved pro-IGIF had no detectable IFN- $\gamma$  inducing activity, ICE-cleaved pro-IGIF was active in inducing  
10 IFN- $\gamma$  production in Th1 cells.

Like ICE, the ICE homolog TX also cleaved pro-IGIF into similarly sized polypeptides. However, its catalytic efficiency was about two orders of magnitude lower than that shown for ICE.

15 Consistent with the observations from the Cos cell experiments above, CPP32 cleaved pro-IGIF at a different site (Asp69-Ile70) and the resulting polypeptides had little IFN- $\gamma$  inducing activity (Fig. 1C). CMH-1 and granzyme B each failed to cleave  
20 pro-IGIF to any significant extent.

Together, these results demonstrate that, both in Cos cells and in vitro, ICE and TX are capable of processing the inactive pro-IGIF precursor at the authentic maturation site to generate a biologically  
25 active IGIF molecule.

#### Processing of Pro-IGIF by ICE Facilitates Its Export

IGIF is produced by activated Kupffer cells and macrophages in vivo and is exported out of the cells upon stimulation by endotoxin (H. Okamura et al.,  
30 Infection and Immunity, 63, p. 3966 (1995); H. Okamura et al., Nature, 378, p. 88 (1995)). We used the Cos cell co-expression system (**Example 23**) to examine



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whether the intracellular cleavage of pro-IGIF by ICE would facilitate the export of mature IGIF from the cell. Such is the case for pro-IL-1 $\beta$  when it is cleaved by ICE into active IL-1 $\beta$  (N.A. Thornberry et al., Nature, 356, p. 768 (1992)).

In **Fig. 2A**, Cos cells transfected with an expression plasmid for pro-IGIF alone (lanes 2 and 6) or in combination with an expression plasmid encoding wild type (lanes 3 and 7) or inactive mutant ICE (lanes 4 and 8) were metabolically labeled with <sup>35</sup>S-methionine (see, **Example 24**). Cell lysates (left) and conditioned medium (right) were immunoprecipitated with an anti-IGIF antiserum. The immunoprecipitated proteins were analyzed by SDS-PAGE and fluorography (**Fig. 2A**).

An 18-kDa polypeptide corresponding in size to mature IGIF was detected in the conditioned medium of Cos cells co-expressing pro-IGIF and ICE, while Cos cells co-expressing pro-IGIF and an inactive ICE mutant (ICE-C285S), or pro-IGIF alone (-) exported only very low levels of pro-IGIF and no detectable mature IGIF. We estimate that about 10% of the mature IGIF was exported from co-transfected cells, while greater than 99% of pro-IGIF was retained within the cells.

We also measured the presence of IFN- $\gamma$  inducing activity in cell lysates and in the conditioned medium of the above transfected cells (see, **Example 24**). IFN- $\gamma$  inducing activity was detected in both cell lysates and the conditioned medium of Cos cells co-expressing pro-IGIF and ICE, but not in cells expressing either pro-IGIF or ICE alone (**Fig. 2B**).

These results indicate that ICE cleavage of pro-IGIF facilitates the export of mature, active IGIF from cells.

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Pro-IGIF is a Physiological Substrate of ICE In Vivo

To study the role of ICE in the proteolytic activation and export of IGIF under physiological conditions, we examined the processing of pro-IGIF and export of mature IGIF from lipopolysaccharide (LPS)-activated Kupffer cells harvested from Propionibacterium acnes-elicited wild type and ICE deficient (ICE-/-) mice (Example 25).

As shown in Fig. 3A, Kupffer cells from ICE-/- mice are defective in the export of IGIF. Kupffer cell lysates of wild type and ICE-/- mice contained similar amounts of IGIF as determined by ELISA. IGIF, however, could be detected only in the conditioned medium of wild type but not of the ICE-/- cells. Thus, ICE-deficient (ICE-/-) mice synthesize pro-IGIF, but fail to export it as extracellular pro-mature IGIF.

To determine whether ICE-deficient (ICE-/-) mice process intracellular pro-IGIF but fail to export IGIF, Kupffer cells from wild type and ICE-/- mice were metabolically labeled with <sup>35</sup>S-methionine and IGIF immunoprecipitation experiments were performed on cell lysates and conditioned media as described in Example 25. These experiments demonstrated that unprocessed pro-IGIF was present in both wild type and ICE-/- Kupffer cells. However, the 18-kDa mature IGIF was present only in the conditioned medium of wild type and not ICE-/- Kupffer cells (Fig. 3B). This shows that active ICE is required in cells for the export of processed IGIF out of the cell.

In addition, conditioned medium from wild type but not from ICE-/- Kupffer cells contained IFN- $\gamma$  inducing activity that was not attributed to the action

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of IL-12 because it was insensitive to a neutralizing anti-IL-12 antibody. The absence of IGIF in the conditioned medium of ICE-/- Kupffer cells is consistent with the finding in Cos cells that the processing of pro-IGIF by ICE is required for the export of active IGIF.

Figs. 3C and 3D show that, *in vivo*, ICE-/- mice have reduced serum levels of IGIF and IFN- $\gamma$ , respectively. Wild type (ICE+/+) and ICE-/- mice (n=3) primed with heat-inactivated *P. acnes* were challenged with LPS (Example 26), and the levels of IGIF (Fig. 3C) and IFN- $\gamma$  (Fig. 3D) in the sera of challenged mice were measured by ELISA three hours after LPS challenge (Example 25).

The sera of ICE-/- mice stimulated by *P. acnes* and LPS contained reduced levels of IGIF (Fig. 3C) and no detectable IFN- $\gamma$  inducing activity in the presence of an anti-IL-12 antibody. The reduced serum levels of IGIF likely accounts for the significantly lower levels of IFN- $\gamma$  in the sera of ICE-/- mice (Fig. 3D), because we have observed no significant difference in the production of IL-12 in ICE-/- mice under these conditions. Consistent with this interpretation is the finding that non-adherent splenocytes from wild type and ICE-/- mice produced similar amounts of IFN- $\gamma$  when stimulated with recombinant active IGIF *in vitro*. Thus the impaired production of IFN- $\gamma$  is not due to any apparent defect in the T cells of the ICE-/- mice.

Taken together, these results establish a critical role for ICE in processing the IGIF precursor and in the export of active IGIF both *in vitro* and *in*

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vivo.

To examine in more detail the relationship between serum levels of IFN- $\gamma$  and ICE activity in vivo, a time course after challenge of wild type and  
5 ICE-deficient mice with LPS was performed (Example 26) (Fig. 4).

Fig. 4 shows a time course increase of serum IFN- $\gamma$  in wild type mice, with sustained levels of  $\geq 17$  ng/ml occurring from 9-18 hrs after LPS challenge.  
10 As predicted by the experiments discussed above, serum IFN- $\gamma$  levels were significantly lower in ICE-/- mice, with a maximum of 2 ng/ml achieved over the same time period, which is approximately 15% of the level observed in wild type mice (Fig. 4).

15 Animals were also observed for clinical signs of sepsis and body temperature was measured at 4-hour intervals in wild type and ICE-/- mice challenged with 30 mg/kg or 100 mg/kg LPS (ICE-/-only). Results in Fig. 4 show that wild type mice experienced a  
20 significant decrease in body temperature (from 36°C to 26°C) within 12 hours of LPS challenge. Signs of clinical sepsis were evident and all animals expired within 24-28 hours.

In contrast, ICE-/- mice challenged with  
25 30 mg/kg LPS experienced only a 3°-4°C decrease in body temperature with minimal signs of distress and with no observed lethality. ICE-/- mice challenged with 100 mg/kg LPS experienced clinical symptoms, a decrease in body temperature, and mortality similar to wild type  
30 mice at the 30 mg/kg LPS dose.

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The ICE Inhibitor Ac-YVAD-CHO is an Equipotent  
Inhibitor of IL-1 $\beta$  and IFN- $\gamma$  Production

Since the processing and secretion of  
5 biologically active IGIF is mediated by ICE, we  
compared the activity of a reversible ICE inhibitor  
(Ac-YVAD-CHO) on IL-1 $\beta$  and IFN- $\gamma$  production in a  
peripheral blood mononuclear cell (PBMC) assay  
(**Examples 27**).

10 Results in **Fig. 5** show a similar potency for  
the ability of the Ac-YVAD-CHO ICE inhibitor to  
decrease IL-1 $\beta$  and IFN- $\gamma$  production in human PBMCs,  
with an IC<sub>50</sub> of 2.5  $\mu$ M for each. Similar results were  
obtained in studies with wild type mouse splenocytes.

15 These findings provide additional evidence  
that pro-IGIF is a physiological substrate for ICE and  
suggest that ICE inhibitors will be useful tools for  
controlling physiological levels of IGIF and IFN- $\gamma$ .

In summary, we have found that ICE controls  
20 IGIF and IFN- $\gamma$  levels in vivo and in vitro and that ICE  
inhibitors can decrease levels of IGIF and IFN- $\gamma$  in  
human cells. These results have been described in co-  
pending United States Application Serial No.  
08/712,878, the disclosure of which is herein  
25 incorporated by reference.

Compositions and Methods

The pharmaceutical compositions and methods  
of this invention will be useful for controlling IL-1,  
IGIF and IFN- $\gamma$  levels in vivo. The methods and  
30 compositions of this invention will thus be useful for  
treating or reducing the advancement, severity of  
effects of IL-1, IGIF- and IFN- $\gamma$ -mediated conditions.

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The compounds of this invention are effective ligands for ICE. Accordingly, these compounds are capable of targeting and inhibiting events in IL-1-, apoptosis-, IGIF-, and IFN- $\gamma$ -mediated diseases, and, thus, the ultimate activity of that protein in inflammatory diseases, autoimmune diseases, destructive bone, proliferative disorders, infectious diseases, and degenerative diseases. For example, the compounds of this invention inhibit the conversion of precursor IL-1 $\beta$  to mature IL-1 $\beta$  by inhibiting ICE. Because ICE is essential for the production of mature IL-1, inhibition of that enzyme effectively blocks initiation of IL-1-mediated physiological effects and symptoms, such as inflammation, by inhibiting the production of mature IL-1. Thus, by inhibiting IL-1 $\beta$  precursor activity, the compounds of this invention effectively function as IL-1 inhibitors.

Similarly, compounds of this invention inhibit the conversion of precursor IGIF to mature IGIF. Thus, by inhibiting IGIF production, the compounds of this invention effectively function as inhibitors of IFN- $\gamma$  production.

Accordingly, one embodiment of this invention provides a method for decreasing IGIF production in a subject comprising the step of administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of an ICE inhibitor and a pharmaceutically acceptable carrier.

Another embodiment of this invention provides a method for decreasing IFN- $\gamma$  production in a subject comprising the step of administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of an ICE inhibitor and a

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pharmaceutically acceptable carrier.

In another embodiment, the methods of this invention comprise the step of administering to a subject a pharmaceutical composition comprising an inhibitor of an ICE-related protease that is capable of cleaving pro-IGIF to active IGIF, and a pharmaceutically acceptable carrier. One such ICE-related protease is TX, as described above. This invention thus provides methods and pharmaceutical compositions for controlling IGIF and IFN- $\gamma$  levels by administering a TX inhibitor.

Other ICE-related proteases capable of processing pro-IGIF into an active IGIF form may also be found. Thus it is envisioned that inhibitors of those enzymes may be identified by those of skill in the art and will also fall within the scope of this invention.

The compounds of this invention may be employed in a conventional manner for the treatment of diseases which are mediated by IL-1, apoptosis, IGIF or IFN- $\gamma$ . Such methods of treatment, their dosage levels and requirements may be selected by those of ordinary skill in the art from available methods and techniques. For example, a compound of this invention may be combined with a pharmaceutically acceptable adjuvant for administration to a patient suffering from an IL-1-, apoptosis-, IGIF- or IFN- $\gamma$ -mediated disease in a pharmaceutically acceptable manner and in an amount effective to lessen the severity of that disease.

Alternatively, the compounds of this invention may be used in compositions and methods for treating or protecting individuals against IL-1-, apoptosis-, IGIF- or IFN- $\gamma$ -mediated diseases over

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extended periods of time. The compounds may be employed in such compositions either alone or together with other compounds of this invention in a manner consistent with the conventional utilization of ICE inhibitors in pharmaceutical compositions. For example, a compound of this invention may be combined with pharmaceutically acceptable adjuvants conventionally employed in vaccines and administered in prophylactically effective amounts to protect individuals over an extended period of time against IL-1-, apoptosis-, IGIF- or IFN- $\gamma$ - mediated diseases.

The compounds of this invention may also be co-administered with other ICE inhibitors to increase the effect of therapy or prophylaxis against various IL-1-, apoptosis-, IGIF- or IFN- $\gamma$ -mediated diseases.

In addition, the compounds of this invention may be used in combination either conventional anti-inflammatory agents or with matrix metalloprotease inhibitors, lipoxigenase inhibitors and antagonists of cytokines other than IL-1 $\beta$ .

The compounds of this invention can also be administered in combination with immunomodulators (e.g., bropirimine, anti-human alpha interferon antibody, IL-2, GM-CSF, methionine enkephalin, interferon alpha, diethylthiocarbamate, tumor necrosis factor, naltrexone and rEPO) or with prostaglandins, to prevent or combat IL-1-mediated disease symptoms such as inflammation.

When the compounds of this invention are administered in combination therapies with other agents, they may be administered sequentially or concurrently to the patient. Alternatively, pharmaceutical or prophylactic compositions according



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to this invention comprise a combination of an ICE inhibitor of this invention and another therapeutic or prophylactic agent.

Pharmaceutical compositions of this invention  
5 comprise any of the compounds of the present invention, and pharmaceutically acceptable salts thereof, with any pharmaceutically acceptable carrier, adjuvant or vehicle. Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the  
10 pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as  $\alpha$ -tocopherol polyethyleneglycol 1000 succinate, or other similar  
15 polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine  
20 sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers,  
25 polyethylene glycol and wool fat. Cyclodextrins such as  $\alpha$ -,  $\beta$ - and  $\gamma$ -cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl- $\beta$ -cyclodextrins, or other solubilized derivatives may also be  
30 advantageously used to enhance delivery of compounds of this invention.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by

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inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. We prefer oral administration. The pharmaceutical compositions of this invention may contain any  
5 conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compounds or  
10 its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

15 The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile  
20 injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a  
25 solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending  
30 medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable

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oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant such as Ph. Helv or a similar alcohol.

5           The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, and aqueous suspensions and  
10       solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral  
15       administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or  
flavoring and/or coloring agents may be added.

20           The pharmaceutical compositions of this invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient  
25       which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

30           Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For application topically to the skin, the pharmaceutical

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composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-administered transdermal patches are also included in this invention.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

Dosage levels of between about 0.01 and about 100 mg/kg body weight per day, preferably between about 1 and 50 mg/kg body weight per day of the active ingredient compound are useful in the prevention and treatment of IL-1-, apoptosis, IGIF and IFN- $\gamma$ -mediated

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diseases, including inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases, degenerative diseases, necrotic diseases, osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, adult respiratory distress syndrome, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, inflammatory bowel disease, Crohn's disease, psoriasis, graft vs. host disease, osteoporosis, multiple myeloma-related bone disorder, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma sepsis, septic shock, Shigellosis, Alzheimer's disease, Parkinson's disease, cerebral ischemia, myocardial ischemia, spinal muscular atrophy, multiple sclerosis, AIDS-related encephalitis, HIV-related encephalitis, aging, alopecia, and neurological damage due to stroke. Typically, the pharmaceutical compositions of this invention will be administered from about 1 to 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Preferably, such preparations contain from about 20% to about 80% active compound.

Upon improvement of a patient's condition, a

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5 maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level, treatment should cease. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence or  
10 disease symptoms.

As the skilled artisan will appreciate, lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of  
15 factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, and the patient's disposition to the  
20 disease and the judgment of the treating physician.

The IL-1 mediated diseases which may be treated or prevented by the compounds of this invention include, but are not limited to, inflammatory diseases, autoimmune diseases, destructive bone disorders,  
25 proliferative disorders, infectious diseases, and degenerative diseases. The apoptosis-mediated diseases which may be treated or prevented by the compounds of this invention include degenerative diseases.

Inflammatory diseases which may be treated or  
30 prevented include, but are not limited to osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, and adult respiratory distress syndrome. Preferably the inflammatory disease is osteoarthritis or acute pancreatitis.

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Autoimmune diseases which may be treated or prevented include, but are not limited to, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, 5 Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, multiple sclerosis, inflammatory bowel disease, 10 Crohn's disease, psoriasis, and graft vs. host disease. Preferably the autoimmune disease is rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, or psoriasis.

Destructive bone disorders which may be treated or prevented include, but are not limited to, 15 osteoporosis and multiple myeloma-related bone disorder.

Proliferative diseases which may be treated or prevented include, but are not limited to, acute 20 myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, and multiple myeloma.

Infectious diseases which may be treated or prevented include, but are not limited to, sepsis, 25 septic shock, and Shigellosis.

The IL-1-mediated degenerative or necrotic diseases which may be treated or prevented by the compounds of this invention include, but are not limited to, Alzheimer's disease, Parkinson's disease, 30 cerebral ischemia, and myocardial ischemia. Preferably, the degenerative disease is Alzheimer's disease.

The apoptosis-mediated degenerative diseases which may be treated or prevented by the compounds of

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this invention include, but are not limited to, Alzheimer's disease, Parkinson's disease, cerebral ischemia, myocardial ischemia, spinal muscular atrophy, multiple sclerosis, AIDS-related encephalitis, HIV-related encephalitis, aging, alopecia, and neurological damage due to stroke.

The methods of this invention may be used for treating, or reducing the advancement, severity or effects of an IGIF-or IFN- $\gamma$ -mediated inflammatory, autoimmune, infectious, proliferative, destructive bone, necrotic, and degenerative conditions, including diseases, disorders or effects, wherein the conditions are characterized by increased levels of IGIF or IFN- $\gamma$  production.

Examples of such inflammatory conditions include, but are not limited to, osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, cerebral ischemia, myocardial ischemia and adult respiratory distress syndrome.

Preferably, the inflammatory condition is rheumatoid arthritis, ulcerative colitis, Crohn's disease, hepatitis and adult respiratory distress syndrome.

Examples of such infectious conditions include, but are not limited to, infectious hepatitis, sepsis, septic shock and Shigellosis.

Examples of such autoimmune conditions include, but are not limited to, glomerulonephritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), juvenile diabetes, autoimmune hemolytic anemia, autoimmune



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neutropenia, thrombocytopenia, myasthenia gravis, multiple sclerosis, psoriasis, lichenplanus, graft vs. host disease, acute dermatomyositis, eczema, primary cirrhosis, hepatitis, uveitis, Behcet's disease, acute  
5 dermatomyositis, atopic skin disease, pure red cell aplasia, aplastic anemia, amyotrophic lateral sclerosis and nephrotic syndrome.

Preferably the autoimmune condition is glomerulonephritis, insulin-dependent diabetes mellitus (Type I), juvenile diabetes, psoriasis, graft vs. host  
10 disease, including transplant rejection, and hepatitis.

Examples of such destructive bone disorders include, but are not limited to, osteoporosis and multiple myeloma-related bone disorder.

15 Examples of such proliferative conditions include, but are not limited to, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, and multiple myeloma.

Examples of such neurodegenerative conditions include, but are not limited to, Alzheimer's disease, Parkinson's disease and Huntington's disease.

Although this invention focuses on the use of the compounds disclosed herein for preventing and treating IL-1, apoptosis, IGIF- and IFN- $\gamma$ -mediated  
25 diseases, the compounds of this invention can also be used as inhibitory agents for other cysteine proteases.

The compounds of this invention are also useful as commercial reagents which effectively bind to ICE or other cysteine proteases. As commercial  
30 reagents, the compounds of this invention, and their derivatives, may be used to block proteolysis of a target peptide in biochemical or cellular assays for ICE and ICE homologs or may be derivatized to bind to a

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stable resin as a tethered substrate for affinity chromatography applications. These and other uses which characterize commercial cystine protease inhibitors will be evident to those of ordinary skill in the art.

#### Process of Preparing N-Acylamino Compounds

The ICE inhibitors of this invention may be synthesized using conventional techniques. Advantageously, these compounds are conveniently synthesized from readily available starting materials.

The compounds of this invention are among the most readily synthesized ICE inhibitors known. Previously described ICE inhibitors often contain four or more chiral centers and numerous peptide linkages. The relative ease with which the compounds of this invention can be synthesized represents an advantage in the large scale production of these compounds.

For example, compounds of this invention may be prepared using the processes described herein. As can be appreciated by the skilled practitioner, these processes are not the only means by which the compounds described and claimed in this application may be synthesized. Further methods will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps described herein may be performed in an alternate sequence or order to give the desired compounds.

This invention also provides a preferred method for preparing the compounds of this invention. Accordingly, in another embodiment (M) is provided a process for preparing an N-acylamino compound comprising the steps of:

a) mixing a carboxylic acid with an N-

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alloc-protected amino in the presence of an inert solvent, triphenylphosphine, a nucleophilic scavenger, and tetrakis-triphenyl phosphine palladium(0) at ambient temperature under an inert atmosphere; and

5           b) adding to the step a) mixture, HOBT and EDC; and optionally comprising the further step of:

          c) hydrolyzing the step b) mixture in the presence of a solution comprising an acid and H<sub>2</sub>O, wherein the step b) mixture is optionally concentrated, prior to hydrolyzing.

10           Preferably, the inert solvent is CH<sub>2</sub>Cl<sub>2</sub>, DMF, or a mixture of CH<sub>2</sub>Cl<sub>2</sub> and DMF.

          Preferably, the nucleophilic scavenger is dimedone, morpholine, trimethylsilyl dimethylamine, or dimethyl barbituric acid. More preferably, the nucleophilic scavenger is trimethylsilyl dimethylamine or dimethyl barbituric acid.

15           Preferably, the solution comprises trifluoroacetic acid in about 1-90% by weight. More preferably, the solution comprises trifluoroacetic acid in about 20-50% by weight.

          Alternatively, the solution comprises hydrochloric acid in about 0.1-30% by weight. More preferably, the solution comprises hydrochloric acid in about 0.1-30% by weight.

25           More preferably, in the above process, the inert solvent is CH<sub>2</sub>Cl<sub>2</sub>, DMF, or a mixture of CH<sub>2</sub>Cl<sub>2</sub> and DMF and the nucleophilic scavenger is dimedone, morpholine, trimethylsilyl dimethylamine, or dimethyl barbituric acid.

30           Most preferably, in the above process the inert solvent is CH<sub>2</sub>Cl<sub>2</sub>, DMF, or a mixture of CH<sub>2</sub>Cl<sub>2</sub> and DMF and the nucleophilic scavenger is trimethylsilyl dimethylamine or dimethyl barbituric acid.

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Preferably, the N-acyclamino compound is represented by formula (VIII):



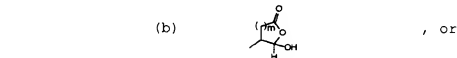
wherein:

R<sub>1</sub> is as defined above in embodiment (A);

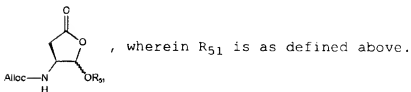
R<sub>2</sub> is:



wherein R<sub>51</sub> is as defined above in embodiment (B);



Preferably, the N-alloc-protected amine is:



20 In preferred processes, the substituents are as defined in embodiment (A).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein R<sub>1</sub> is as defined

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above in embodiment (B) and  $R_2$  is as defined above in embodiment (M).

Preferably in these alternative processes, the substituents are as defined above in  
5 embodiment (B).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein  $R_1$  is as defined above in embodiment (C) and  $R_2$  is as defined above in  
10 embodiment (M).

Preferably in these alternative processes, the substituents are as defined above in  
embodiment (C).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein  $R_1$  is as defined  
15 above in embodiment (D) and  $R_2$  is as defined above in embodiment (M).

Preferably in these alternative processes, the substituents are as defined above in  
embodiment (D).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein  $R_1$  is as defined  
20 above in embodiment (E) and  $R_2$  is as defined above in embodiment (M).

Preferably in these alternative processes, the substituents are as defined above in  
25 embodiment (E).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein  $R_1$  is as defined  
above in embodiment (F) and  $R_2$  is as defined above in  
30 embodiment (M).

Preferably in these alternative processes, the substituents are as defined above in  
embodiment (F).

Alternatively, the N-acylamino compound is

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represented by formula (VIII), wherein  $R_1$  is as defined above in embodiment (G) and  $R_2$  is as defined above in embodiment (G).

Preferably in these alternative  
5 processes, the substituents are as defined above in embodiment (G).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein  $R_1$  is as defined above in embodiment (H) and  $R_2$  is as defined above in  
10 embodiment (M).

Preferably in these alternative processes, the substituents are as defined above in embodiment (H).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein  $R_1$  is as defined above in embodiment (I) and  $R_2$  is as defined above in  
15 embodiment (M).

Preferably in these alternative processes, the substituents are as defined above in  
20 embodiment (I).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein  $R_1$  is as defined above in embodiment (J) and  $R_2$  is as defined above in  
embodiment (M).

Preferably in these alternative  
25 processes, the substituents are as defined above in embodiment (J).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein  $R_1$  is as defined  
30 above in embodiment (K) and  $R_2$  is as defined above in embodiment (M).

Preferably in these alternative processes, the substituents are as defined above in  
embodiment (K).

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Alternatively, the N-acylamino compound is represented by formula (VIII), wherein  $R_1$  is as defined above in embodiment (L) and  $R_2$  is as defined above in embodiment (M).

5                    Preferably in these alternative processes, the substituents are as defined above in embodiment (L).

                  In order that this invention be more fully understood, the following examples are set forth.  
10    These examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way.

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Example 1

Inhibition of ICE

We obtained inhibition constants ( $K_i$ ) and  $IC_{50}$  values for compounds of this invention using the three methods described below:

1. Enzyme assay with UV-visible substrate

This assay is run using an Succinyl-Tyr-Val-Ala-Asp-pNitroanilide substrate. Synthesis of analogous substrates is described by L. A. Reiter (Int.

10 J. Peptide Protein Res. 43, 87-96 (1994)). The assay mixture contains:

65  $\mu$ l buffer (10mM Tris, 1 mM DTT, 0.1% CHAPS (pH 8.1)  
10  $\mu$ l ICE (50 nM final concentration to give a rate of  
~1mOD/min)

15 5  $\mu$ l DMSO/Inhibitor mixture  
20  $\mu$ l 400 $\mu$ M Substrate (80  $\mu$ M final concentration)  
100 $\mu$ l total reaction volume

The visible ICE assay is run in a 96-well microtiter plate. Buffer, ICE and DMSO (if inhibitor  
20 is present) are added to the wells in the order listed. The components are left to incubate at room temperature for 15 minutes starting at the time that all components are present in all wells. The microtiter plate reader is set to incubate at 37 °C. After the 15 minute  
25 incubation, substrate is added directly to the wells and the reaction is monitored by following the release of the chromophore (pNA) at 405 - 603 nm at 37 °C for 20 minutes. A linear fit of the data is performed and the rate is calculated in mOD/min. DMSO is only  
30 present during experiments involving inhibitors, buffer is used to make up the volume to 100  $\mu$ l in the other experiments.



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## 2. Enzyme Assay with Fluorescent Substrate

This assay is run essentially according to Thornberry et al. (Nature 356: 768-774 (1992)), using substrate 17 referenced in that article. The substrate is: Acetyl-Tyr-Val-Ala-Asp-amino-4-methylcoumarin (AMC). The following components are mixed:

- 65  $\mu$ l buffer (10mM Tris, 1mM DTT, 0.1% CHAPS @pH8.1)
- 10  $\mu$ l ICE (2 - 10 nM final concentration)
- 5  $\mu$ l DMSO/inhibitor solution
- 10 20  $\mu$ l 150  $\mu$ M Substrate (30  $\mu$ M final)
- 100  $\mu$ l total reaction volume

The assay is run in a 96 well microtiter plate. Buffer and ICE are added to the wells. The components are left to incubate at 37 °C for 15 minutes in a temperature-controlled wellplate. After the 15 minute incubation, the reaction is started by adding substrate directly to the wells and the reaction is monitored @37 °C for 30 minutes by following the release of the AMC fluorophore using an excitation wavelength for 380 nm and an emission wavelength of 460 nm. A linear fit of the data for each well is performed and a rate is determined in fluorescence units per second.

For determination of enzyme inhibition constants ( $K_i$ ) or the mode of inhibition (competitive, uncompetitive or noncompetitive), the rate data determined in the enzyme assays at varying inhibitor concentrations are computer-fit to standard enzyme kinetic equations (see I. H. Segel, Enzyme Kinetics, Wiley-Interscience, 1975).

The determination of second order rate constants for irreversible inhibitors was performed by fitting the fluorescence vs time data to the progress equations of Morrison. Morrison, J.F., Mol. Cell.

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Biophys., 2, pp. 347-368 (1985). Thornberry et al. have published a description of these methods for measurement of rate constants of irreversible inhibitors of ICE. Thornberry, N.A., et al.

- 5 Biochemistry, 33, pp. 3923-3940 (1994). For compounds where no prior complex formation can be observed kinetically, the second order rate constants ( $k_{inact}$ ) are derived directly from the slope of the linear plots of  $k_{obs}$  vs.  $[I]$ . For compounds where prior complex  
10 formation to the enzyme can be detected, the hyperbolic plots of  $k_{obs}$  vs.  $[I]$  are fit to the equation for saturation kinetics to first generate  $K_i$  and  $k'$ . The second order rate constant  $k_{inact}$  is then given by  $k'/K_i$ .

15 3. PBMC Cell assay

IL-1 $\beta$  Assay with a Mixed Population of Human  
Peripheral Blood Mononuclear Cells (PBMC)  
or Enriched Adherent Mononuclear Cells

- Processing of pre-IL-1 $\beta$  by ICE can be  
20 measured in cell culture using a variety of cell sources. Human PBMC obtained from healthy donors provides a mixed population of lymphocyte subtypes and mononuclear cells that produce a spectrum of  
interleukins and cytokines in response to many classes  
25 of physiological stimulators. Adherent mononuclear cells from PBMC provides an enriched source of normal monocytes for selective studies of cytokine production by activated cells.

Experimental Procedure:

- 30 An initial dilution series of test compound in DMSO or ethanol is prepared, with a subsequent dilution into RPMI-10% FBS media (containing 2 mM L-glutamine, 10 mM HEPES, 50 U and 50 ug/ml pen/strep)

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respectively to yield drugs at 4x the final test concentration containing 0.4% DMSO or 0.4% ethanol. The final concentration of DMSO is 0.1% for all drug dilutions. A concentration titration which brackets the apparent  $K_i$  for a test compound determined in an ICE inhibition assay is generally used for the primary compound screen.

Generally 5-6 compound dilutions are tested and the cellular component of the assay is performed in duplicate, with duplicate ELISA determinations on each cell culture supernatant.

#### FBMC Isolation and IL-1 Assay:

Buffy coat cells isolated from one pint human blood (yielding 40-45 ml final volume plasma plus cells) are diluted with media to 80 ml and LeukoPREP separation tubes (Becton Dickinson) are each overlaid with 10 ml of cell suspension. After 15 min centrifugation at 1500-1800 xg, the plasma/media layer is aspirated and then the mononuclear cell layer is collected with a Pasteur pipette and transferred to a 15 ml conical centrifuge tube (Corning). Media is added to bring the volume to 15 ml, gently mix the cells by inversion and centrifuge at 300 xg for 15 min. Resuspend the FBMC pellet in a small volume of media, count cells and adjust to  $6 \times 10^6$  cells/ml.

For the cellular assay, 1.0 ml of the cell suspension is added to each well of a 24-well flat bottom tissue culture plate (Corning), 0.5 ml test compound dilution and 0.5 ml LPS solution (Sigma #L-3012; 20 ng/ml solution prepared in complete RPMI media; final LPS concentration 5 ng/ml). The 0.5 ml additions of test compound and LPS are usually sufficient to mix the contents of the wells. Three control mixtures are run per experiment, with either

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LPS alone, solvent vehicle control, and/or additional media to adjust the final culture volume to 2.0 ml. The cell cultures are incubated for 16-18 hr at 37 °C in the presence of 5% CO<sub>2</sub>.

5       At the end of the incubation period, cells are harvested and transferred to 15 ml conical centrifuge tubes. After centrifugation for 10 min at 200 xg, supernatants are harvested and transferred to 1.5 ml Eppendorf tubes. It may be noted that the cell  
10 pellet may be utilized for a biochemical evaluation of pre-IL-1 $\beta$  and/or mature IL-1 $\beta$  content in cytosol extracts by western blotting or ELISA with pre-IL-1 $\beta$  specific antisera.

#### Isolation of Adherent Mononuclear cells:

15       PBMC are isolated and prepared as described above. Media (1.0 ml) is first added to wells followed by 0.5 ml of the PBMC suspension. After a one hour incubation, plates are gently shaken and nonadherent cells aspirated from each well. Wells are then gently  
20 washed three times with 1.0 ml of media and final resuspended in 1.0 ml media. The enrichment for adherent cells generally yields 2.5-3.0 x 10<sup>5</sup> cells per well. The addition of test compounds, LPS, cell incubation conditions and processing of supernatants  
25 proceeds as described above.

#### ELISA:

We have used Quantikine kits (R&D Systems) for measurement of mature IL-1 $\beta$ . Assays are performed according to the manufacturer's directions. Mature  
30 IL-1 $\beta$  levels of about 1-3 ng/ml in both PBMC and adherent mononuclear cell positive controls are observed. ELISA assays are performed on 1:5, 1:10 and 1:20 dilutions of supernatants from LPS-positive

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controls to select the optimal dilution for supernatants in the test panel.

The inhibitory potency of the compounds can be represented by an  $IC_{50}$  value, which is the  
5 concentration of inhibitor at which 50% of mature IL-1 $\beta$  is detected in the supernatant as compared to the positive controls.

The skilled practitioner realizes that values obtained in cell assays, such as those described  
10 herein, can depend on multiple factors, such as cell type, cell source, growth conditions and the like.

#### Example 2

##### Pharmacokinetic Studies in the Mouse

15 Peptidyl ICE inhibitors are cleared rapidly with clearance rates greater than 100  $\mu$ /min/kg. Compounds with lower clearance rates have improved pharmacokinetic properties relative to peptidyl ICE inhibitors.

20 We obtained the rate of clearance in the mouse ( $\mu$ /min/kg) for several compounds of this invention using the method described below:

##### Sample Preparation and Dosing

Compounds were dissolved in sterile TRIS  
25 solution (0.02M or 0.05M) at a concentration of 2.5mg/ml. Where necessary to ensure a complete solution, the sample was first dissolved in a minimum of dimethylacetamide (maximum of 5% of total solution volume) then diluted with the TRIS solution.

30 The drug solution was administered to CD-1 mice (Charles River Laboratories - 26-31g) via the tail

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vein at a dose volume of 10ml/kg giving a drug dose of 25mg/kg.

Mice were dosed in groups of 5 for each timepoint (generally from 2 minutes to 2 hours) then at the appropriate time the animals were anaesthetised with halothane and the blood collected into individual heparinized tubes by jugular severance. The blood samples were cooled to 0 °C then the plasma separated and stored at -20 °C until assayed.

#### 10 Bioassay

Drug concentration in the plasma samples were determined by HPLC analysis with UV or MS (ESP) detection. Reverse phase chromatography was employed using a variety of bonded phases from C1 to C18 with eluents composed of aqueous buffer/acetonitrile mixtures run under isocratic conditions.

Quantitation was by external standard methods with calibration curves constructed by spiking plasma with drug solutions to give concentrations in the range of 0.5 to 50µg/ml.

Prior to analysis the plasma samples were deproteinated by the addition of acetonitrile, methanol, trichloroacetic acid or perchloric acid followed by centrifugation at 10,000g for 10 minutes. Sample volumes of 20µl to 50µl were injected for analysis.

#### Compound 214e

##### Dosing and sampling

The drug was dissolved in sterile 0.02M Tris to give a 2.5mg/ml solution which was administered to 11 groups of 5 male CD-1 mice via the tail vein at a dose of 25mg/kg. At each of the following timepoints: 2, 5, 10, 15, 20, 30, 45, 60, 90 and 120 minutes a

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group of animals was anaesthetised and the blood collected into heparinized tubes. After separation the plasma was stored at -20 °C until assayed.

#### Assay

- 5 Aliquots of plasma (150µl) were treated with 5% perchloric acid (5µl) then mixed by vortexing and allowed to stand for 90 minutes prior to centrifugation. The resulting supernatant was separated and 20µl was injected for HPLC analysis.

#### 10 HPLC Conditions

|              |                         |                     |
|--------------|-------------------------|---------------------|
| Column       | 100 x 4.6mm             | Kromasil KR 100 5C4 |
| Mobile Phase | 0.1M Tris pH7.5         | 86%                 |
|              | Acetonitrile            | 14%                 |
| Flowrate     | 1ml/min                 |                     |
| 15 Detection | UV at 210nm             |                     |
|              | Retention Time 3.4 mins |                     |

The results of the analysis indicated a decrease in the mean plasma level of the drug from ~ 70µg/ml at 2 minutes to < 2µg/ml at 90 and 120 minutes.

#### 20 Compound 217e

##### Dosing and sampling

- The drug was dissolved in sterile 0.02M Tris to give a 2.5mg/ml solution which was administered to 11 groups of 5 male CD-1 mice via the tail vein at a
- 25 dose of 25mg/kg. At each of the following timepoints: 2, 5, 10, 15, 20, 30, 45, 60, 90 and 120 minutes a group of animals was anaesthetised and the blood collected into heparinized tubes. After separation the plasma was stored at -20 °C until assayed.

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Assay

Aliquots of plasma (100 $\mu$ l) were diluted with acetonitrile (100 $\mu$ l) then mixed by vortexing for 20 seconds before centrifugation for 10 minutes. The  
5 resulting supernatant was separated and 20 $\mu$ l was injected for HPLC analysis.

HPLC Conditions

|                |                                  |             |
|----------------|----------------------------------|-------------|
| Column         | 150 x 4.6mm                      | Zorbax SBC8 |
| Mobile Phase   | 0.05M Phosphate                  | 72%         |
| 10             | buffer pH7.1                     |             |
|                | Acetonitrile                     | 28%         |
| Flowrate       | 1.4ml/min                        |             |
| Detection      | UV at 210nm                      |             |
| Retention Time | 3.0 and 3.6 mins (diastereomers) |             |

15 The results of the analysis indicated a decrease in mean plasma concentrations from ~ 55 $\mu$ g/ml at 2 minutes to < 0.2 $\mu$ g/ml at 60-120 minutes.

Example 3

Peptidyl ICE inhibitors are cleared rapidly  
20 with clearance rates greater than 80 ml/min/kg. Compounds with lower clearance rates have improved pharmacokinetic properties relative to peptidyl ICE inhibitors.

We obtained the rate of clearance in the rat  
25 (ml/min/kg) for several compounds of this invention using the method described below:

In vivo Rat Clearance Assay

Cannulations of the jugular and carotid vessels of rats under anesthesia were performed one day  
30 prior to the pharmacokinetic study. M.J. Free, R.A.



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Jaffee; 'Cannulation techniques for the collection of blood and other bodily fluids'; in: Animal Models; p. 480-495; N.J. Alexander, Ed.; Academic Press; (1978). Drug (10mg/mL) was administered via the jugular vein in a vehicle usually consisting of: propylene glycol/saline, containing 100mM sodium bicarbonate in a 1:1 ratio. Animals were dosed with 10-20 mg drug/kg and blood samples were drawn at 0, 2, 5, 7, 10, 15, 20, 30, 60, and 90 minutes from an indwelling carotid catheter. The blood was centrifuged to plasma and stored at -20 °C until analysis. Pharmacokinetic analysis of data was performed by non-linear regression using standard software such as RStrip (MicroMath Software, UT) and/or Pcnnonlin (SCI Software, NC) to obtain clearance values.

#### Analytical:

Rat plasma was extracted with an equal volume of acetonitrile (containing 0.1% TFA). Samples were then centrifuged at approximately 1,000 x g and the supernatant analyzed by gradient HPLC. A typical assay procedure is described below.

200 µL of plasma was precipitated with 200 µL of 0.1% trifluoroacetic acid (TFA) in acetonitrile and 10 µL of a 50% aqueous zinc chloride solution, vortexed then centrifuged at ~1000 x g and the supernatant collected and analyzed by HPLC.

#### HPLC procedure:

|                        |  |
|------------------------|--|
| Column:                | Zorbax SB-CN (4.6 x 150 mm) (5µ particle size) |
| 30 Column temperature: | 50 °C  |
| Flow rate:             | 1.0 mL/min                                     |
| Injection volume:      | 75 µL  |
| Mobile phase:          | A=0.1% TFA in water and B=100% acetonitrile    |

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Gradient employed: 100% A to 30% A in 15.5 min  
0% A at 16 min  
100% A at 19.2 min  
Wavelength: 214 nm

- 5                   A standard curve was run at 20, 10, 5, 2 and  
1 µg/mL concentrations.

#### Example 4

##### Whole Blood Assay for IL-1 $\beta$ Production

- 10                   We obtained IC<sub>50</sub> values for several compounds  
of this invention using the method described below:

##### Purpose:

- 15                   The whole blood assay is a simple method for  
measuring the production of IL-1 $\beta$  (or other cytokines)  
and the activity of potential inhibitors. The  
complexity of this assay system, with its full  
complement of lymphoid and inflammatory cell types,  
spectrum of plasma proteins and red blood cells is an  
ideal in vitro representation of human in vivo  
physiologic conditions.

##### 20 Materials:

- Pyrogen-free syringes (~ 30 cc)  
Pyrogen-free sterile vacuum tubes containing  
lyophilized Na<sub>2</sub>EDTA (4.5 mg/10 ml tube)  
Human whole blood sample (~ 30-50 cc)  
25 1.5 ml eppendorf tubes  
Test compound stock solutions (~ 25mM in DMSO or other  
solvent)  
Endotoxin-free sodium chloride solution (0.9%) and HBSS  
Lipopolysaccharide (Sigma; Cat.# L-3012) stock solution  
30 at 1mg/ml in HBSS

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IL-1 $\beta$  ELISA Kit (R & D Systems; Cat # DLB50)

TNF $\alpha$  ELISA Kit (R & D Systems; Cat # DTA50)

Water bath or incubator

Whole Blood Assay Experimental Procedure:

- 5           Set incubator or water bath at 30 °C.  
Aliquot 0.25ml of blood into 1.5 ml eppendorf tubes.  
**Note:** be sure to invert the whole blood sample tubes  
after every two aliquots. Differences in replicates  
may result if the cells sediment and are not uniformly  
10 suspended. Use of a positive displacement pipette will  
also minimize differences between replicate aliquots.

- Prepare drug dilutions in sterile pyrogen-  
free saline by serial dilution. A dilution series  
which brackets the apparent  $K_i$  for a test compound  
15 determined in an ICE inhibition assay is generally used  
for the primary compound screen. For extremely  
hydrophobic compounds, we have prepared compound  
dilutions in fresh plasma obtained from the same blood  
donor or in PBS-containing 5% DMSO to enhance  
20 solubility.

- Add 25  $\mu$ l test compound dilution or vehicle  
control and gently mix the sample. Then add 5.0  $\mu$ l LPS  
solution (250 ng/ml stocked prepared fresh: 5.0 ng/ml  
final concentration LPS), and mix again. Incubate the  
25 tubes at 30 °C in a water bath for 16-18 hr with  
occasional mixing. Alternatively, the tubes can be  
placed in a rotator set at 4 rpm for the same  
incubation period. This assay should be set up in  
duplicate or triplicate with the following controls:  
30 negative control- no LPS; positive control- no test  
inhibitor; vehicle control- the highest concentration  
of DMSO or compound solvent used in the experiment.

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Additional saline is added to all control tubes to normalize volumes for both control and experimental whole blood test samples

After the incubation period, whole blood .  
5 samples are centrifuged for 10 minutes at ~ 2000 rpm in the microfuge, plasma is transferred to a fresh microfuge tube and centrifuged at 1000 x g to pellet residual platelets if necessary. Plasma samples may be stored frozen at -70 °C prior to assay for cytokine  
10 levels by ELISA.

#### ELISA:

We have used R & D Systems (614 McKinley Place N.E. Minneapolis, MN 55413) Quantikine kits for measurement of IL-1 $\beta$  and TNF- $\alpha$ . The assays are  
15 performed according to the manufacturer's directions. We have observed IL-1 $\beta$  levels of ~ 1-5 ng/ml in positive controls among a range of individuals. A 1:200 dilution of plasma for all samples has been sufficient in our experiments for ELISA results to fall  
20 on the linear range of the ELISA standard curves. It may be necessary to optimize standard dilutions if you observe differences in the whole blood assay. Nerad, J.L. et al., J. Leukocyte Biol., 52, pp. 687-692 (1992).

#### 25 Example 5

##### Inhibition of ICE homologs

#### 1. Isolation of ICE homologs

Expression of TX in insect cells using a baculovirus expression system. We have subcloned Tx cDNA (Faucheu  
30 et al., supra 1995) into a modified pVL1393 transfer

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vector, co-transfected the resultant plasmid (pVL1393/TX) into insect cells with viral DNA and identified the recombinant baculovirus. After the generation of high titer recombinant virus stock, the medium was examined for TX activity using the visible ICE assay. Typically, infection of *Spodoptera frugiperda* (Sf9) insect cells at an MOI of 5 with recombinant virus stock resulted in a maximum expression after 48 hours of 4.7µg/ml. ICE was used as a standard in the assay.

Amino terminal T7 tagged versions of ICE or TX were also expressed. Designed originally to assist the identification and purification of the recombinant proteins, the various constructs have also allowed examination of different levels of expression and of the relative levels of apoptosis experienced by the different homologs. Apoptosis in the infected Sf9 cells (examined using a Trypan Blue exclusion assay) was increased in the lines expressing ICE or TX relative to cells infected with the viral DNA alone.

**Expression and purification of N-terminally (His)<sub>6</sub>-tagged CPP32 in *E. coli*.** A cDNA encoding a CPP32 (Fernandes-Alnemri et al, supra 1994) polypeptide starting at Ser (29) was PCR amplified with primers that add in frame XhoI sites to both the 5' and 3' ends of the cDNA and the resulting XhoI fragment ligated into a Xho I-cut pET-15b expression vector to create an in frame fusion with (his)<sub>6</sub> tag at the n-terminus of the fusion protein. The predicted recombinant protein starts with the amino acid sequence of MGSSHHHHHHSSGLVPRGSHMLE, where LVPRGS represents a thrombin cleavage site, followed by CPP32 starting at

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Ser (29). *E. coli* BL21(DE3) carrying the plasmid were grown to log phase at 30 °C and were then induced with 0.8 mM IPTG. Cells were harvested two hours after IPTG addition. Lysates were prepared and soluble proteins were purified by Ni-agarose chromatography. All of the expressed CPP32 protein was in the processed form. N-terminal sequencing analysis indicated that the processing occurred at the authentic site between Asp (175) and Ser (176). Approximately 50 µg of CPP32 protein from 200 ml culture. As determined by active site titration, the purified proteins were fully active. The protease preparation were also very active in vitro in cleaving PARP as well as the synthetic DEVD-AMC substrate (Nicholson et al, supra 1995).

## 2. Inhibition of ICE homologs

The selectivity of a panel of reversible inhibitors for ICE homologs is depicted in Table 1. ICE enzyme assays were performed according to Wilson et al (supra 1994) using a YVAD-AMC substrate (Thornberry et al, supra 1992). Assay of TX activity was performed using the ICE substrate under identical conditions to ICE. Assay of CPP32 was performed using a DEVD-AMC substrate (Nicholson et al., supra 1995). In general, there is low selectivity between ICE and TX for a wide range of scaffolds. None of the synthetic ICE compounds tested are effective inhibitors of CPP32. Assay of the reversible compounds at the highest concentration (1 µM) revealed no inhibition.

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Table 1

| Compound | $K_i$ ICE (nM) | $K_i$ TX (nM) | $K_i$ CPP32 (nM) |
|----------|----------------|---------------|------------------|
| 214e     | 7.5            | $7.0 \pm 1.1$ | > 1000           |
| 135a     | 90             | $55 \pm 9$    | >1000            |
| 5 125b   | 60             | $57 \pm 13$   | > 1000           |
| 137      | 40             | $40 \pm 7$    | > 1000           |

Second-order rate constants for inactivation of ICE and ICE homologs with selected irreversible inhibitors are presented below (Table 2). The irreversible compounds studied are broad spectrum inhibitors of ICE and its homologs. Some selectivity, however, is observed with the irreversible compounds comparing inhibition of ICE and CPP32.

Table 2

| Compound | $k_{inact}$<br>(ICE)<br>$M^{-1} s^{-1}$ | $k_{inact}$ (TX)<br>$M^{-1} s^{-1}$ | $k_{inact}$<br>(CPP32)<br>$M^{-1} s^{-1}$ |
|----------|---|-------------------------------------|---|
| 138      | 120,000                                 | 150,000                             | 550,000                                   |
| 217d     | 475,000                                 | 250,000                             | 150,000                                   |
| 108a     | 100,000                                 | 25,000                              | nd  |

Example 620 Inhibition of apoptosis

**Fas-Induced Apoptosis in U937 cells.** Compounds were evaluated for their ability to block anti-Fas-induced apoptosis. In a preliminary experiment using RT-PCR, we detected mRNA encoding ICE, TX, ICH-1, CPP32 and

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CMH-1 in unstimulated U937 cells. We used this cell line for apoptosis studies. U937 cells were seeded in culture at  $1 \times 10^5$  cells/ml and grown to  $\sim 5 \times 10^6$  cells/ml. For apoptosis experiments,  $2 \times 10^6$  cells were plated in 24-well tissue culture plates in 1 ml RPMI-1640-10% FBS and stimulated with 100 ng/ml anti-Fas antigen antibody (Medical and Biological Laboratories, Ltd.). After a 24 hr incubation at 37 °C, the percentage of apoptotic cells was determined by FACS analysis using ApoTag reagents.

All compounds were tested initially at 20  $\mu$ M and titrations were performed with active compounds to determine IC<sub>50</sub> values. Inhibition of apoptosis (> 75% at 20  $\mu$ M) was observed for 108a, 136, and 138. An IC<sub>50</sub> of 0.8  $\mu$ M was determined for 217e compared to no inhibition of anti-Fas-induced apoptosis by 214e at 20  $\mu$ M.

#### Example 7

##### In vivo acute assay for efficacy as anti-inflammatory agent

#### **LPS-Induced IL-1 $\beta$ Production.**

Efficacy of 214e and 217e was evaluated in CD1 mice (n=6 per condition) challenged with LPS (20 mg/kg IP). The test compounds were prepared in olive oil:DMSO:ethanol (90:5:5) and administered by IP injection one hour after LPS. Blood was collected seven hours after LPS challenge. Serum IL-1 $\beta$  levels were measure by ELISA. Results in Fig. 6 show a dose dependent inhibition of IL-1 $\beta$  secretion by 214e, with



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an ED<sub>50</sub> of approximately 15 mg/kg. Similar results were obtained in a second experiment. A significant inhibition of IL-1 $\beta$  secretion was also observed in 217e treated mice (Fig. 7). However, a clear dose response was not apparent.

Compounds 214e and 217e (50 mg/kg) were also administered by oral gavage to assess absorption. Results in Fig. 8 show that 214e, but not 217e when administered orally inhibited IL-1 $\beta$  secretion, suggesting potential for oral efficacy of ICE inhibitors as anti-inflammatory agents.

The efficacy of analogs of 214e were also evaluated in LPS challenged mice after IP administration (Fig. 9) and PO administration (Fig. 10).

Table 3 % Inhibition of IL- $\beta$  production by analogs of 214e in LPS-challenged mice after PO and IP administration (50 mg/kg).

Table 3

| Compound | PO%<br>Inhibition | IP%<br>Inhibition |
|----------|-------------------|-------------------|
| 214e     | 75                | 78                |
| 265      | 27                | 30                |
| 416      | 52                | 39                |
| 434      | 80                | 74                |
| 438      | 13                | 40                |
| 442      | 10                | 0                 |
| 2002     | -                 | 78                |

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Table 4

Comparison of 214e Prodrugs for  
Efficacy in LPS Challenged Mice:  
Time Course Inhibition of IL-1 $\beta$  Production

|    |          | Time of Compound Administration<br>(relative to time of LPS challenge, PO, 50 mg/kg) |       |      |       |
|----|----------|--|-------|------|-------|
|    | Compound | -2 hr  | -1 hr | 0 hr | +1 hr |
| 5  | 214e     | 39*  | ~*    | 80*  | 55%   |
|    |          | 43*  | 44*   | 48*  | 75*   |
|    |          | ~*   | ~*    | ~*   | 11*   |
|    |          |  |       |      | 47*   |
|    | 304a     | 30   | 33    | 68   | 37    |
|    | 2100e    | 49   | 54    | 94   | 66    |
|    | 2100a    | 8  | 71    | 67   | 58    |
| 10 | 213e     | 0  | 48    | 41   | 89    |
|    |          | 302  | 0     | 27   | 21    |
|    |          | 2100c  | 0     | 0    | 85    |
|    |          | 2100d  | 42    | 35   | 52    |
|    | 2100b    | 0  | 0     | 47   | 26    |
| 15 | 2001     | ~63  | ~62   | ~57  | ~54   |
|    |          | 64*  | 62*   | 58*  | 55*   |

\* Values obtained in subsequent assays

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Example 8Measurement of blood levels of prodrugs of 214e.

Mice were administered a p.o. dose of compounds **302** and **304a** (50 mg/kg) prepared in 0.5 % carboxymethylcellulose. Blood samples were collected at 1 and 7 hours after dosing. Serum was extracted by precipitation with an equal volume of acetonitrile containing 2 % formic acid followed by centrifugation. The supernatant was analyzed by liquid chromatography-mass spectrometry (ESI-MS) with a detection level of 0.03 to 3 µg/ml. Compounds **302** and **304a** showed detectable blood levels when administered orally, **214e** itself shows no blood levels above 0.10 µg/mL when administered orally. Compounds **302** and **304a** are prodrugs of **214e** and are metabolized to **214e in vivo** (see Fig. 11).

Example 9

We obtained the following data (see Tables 5 and 6) for compounds of this invention using the methods described in Examples 1-8. The structures of the compounds of Example 9 are shown in Example 10-17.

Table 5

| Compound    | UV-Visible<br>K <sub>1</sub> (nM) | Cell<br>PBMC<br>avg.<br>IC50<br>(nM) | Whole<br>human<br>blood<br>IC50<br>(nM) | Clearance<br>Mouse,<br>i.v.<br>ml/min/kg | Clearance<br>Rat, i.v.<br>ml/min/kg |
|-------------|-----------------------------------|--------------------------------------|---|--|-------------------------------------|
| <b>47b</b>  | 27                                | 1800                                 | <600                                    | 338                                      |                                     |
| <b>47a</b>  | 19                                | 2600                                 | 5100                                    | 79                                       | 32                                  |
| <b>135a</b> | 90                                | 2800                                 | 5000                                    | >100                                     |                                     |

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|    | Compound | UV-Visible<br>Ki (nM) | Cell<br>PBMC<br>avg.<br>IC50<br>(nM) | Whole<br>human<br>blood<br>IC50<br>(nM) | Clearance<br>Mouse,<br>i.v.,<br>ml/min/kg | Clearance<br>Rat, i.v.,<br>ml/min/kg |
|----|----------|-----------------------|--------------------------------------|---|---|--------------------------------------|
|    | 135b     | 320                   | 1600                                 | 1700                                    |   |                                      |
|    | 125b     | 60                    | 800                                  | 4500                                    |   |                                      |
|    | 108b     | 400                   | 25000                                |   |   | >100                                 |
|    | 137      | 40                    | 1700                                 | 14000                                   |   |                                      |
| 5  | 139      | 350                   | 2000                                 |   |   |                                      |
|    | 213e     | 130                   | 900                                  | 600<br>400*                             |   |                                      |
|    | 214c     | 1200                  | 5000                                 |   |   |                                      |
|    | 214e     | 7.5                   | 1600                                 | 1300                                    | 23  | 12                                   |
|    | 217c     |                       | 1700                                 | 7000                                    | 70  |                                      |
| 10 | 217e     |                       | 175                                  | 2000                                    | >50                                       |                                      |
|    | 220b     | 600                   | 2125                                 |   |   |                                      |
|    | 223b     | 99                    | 5000                                 |   | >100                                      |                                      |
|    | 223e     | 1.6                   | 3000                                 | >20000                                  | 89  |                                      |
|    | 226e     | 15                    | 1100                                 | 1800                                    | 109                                       |                                      |
| 15 | 227e     | 7                     | 234                                  | 550                                     |   |                                      |
|    | 230e     |                       | 325                                  | 300                                     | 67  |                                      |
|    | 232e     | 1100                  | 4500                                 |   | 22  | 26                                   |
|    | 235e     | 510                   | 4750                                 |   | 36  |                                      |
|    | 238e     | 500                   | 4250                                 |   |   |                                      |
| 20 | 246      | 12                    | 950                                  | 10000                                   | 31  |                                      |
|    | 257      | 13                    | 11000<br>6600*                       |   |   |                                      |
|    | 265      | 47                    | 4300                                 | 1400                                    | 23  | 20                                   |
|    | 281      | 50                    | 600<br>2500*                         |   |   |                                      |
|    | 302      | 4500                  | >20000                               | >20000                                  |   |                                      |
| 25 | 304a     | 200                   | 1,400                                | 2400<br>14000*                          |   |                                      |
|    | 307a     | 55                    | 14500                                | 16000                                   |   |                                      |
|    | 307b     | 165                   |                                      | 14000                                   |   |                                      |
|    | 404      | 2.9                   | 1650<br>1800*                        | 1100                                    | 64  | 24                                   |
|    | 405      | 6.5                   | 1700                                 | 2100                                    |   |                                      |
| 30 | 406      | 4                     | 1650                                 | 2300                                    |   |                                      |
|    | 407      | 0.4                   | 540                                  | 1700                                    |   |                                      |
|    | 408      | 0.5                   | 1100                                 | 1000                                    | 41  | 23                                   |

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| Compound | UV-Visible<br>K1 (nM) | Cell<br>PBMC<br>avg.<br>IC50<br>(nM) | Whole<br>human<br>blood<br>IC50<br>(nM) | Clearance<br>Mouse,<br>i.v.<br>ml/min/kg | Clearance<br>Rat, i.v.<br>ml/min/kg |
|----------|-----------------------|--------------------------------------|---|--|-------------------------------------|
| 409      | 3.7                   | 2500                                 |   |  |                                     |
| 410      | 17                    | 2000                                 | 2800                                    | 32                                       | 20                                  |
| 411      | 0.9                   | 540                                  | 1900                                    |  |                                     |
| 412      | 1.3                   | 580<br>660*                          | 700<br>1000*                            |  | 25                                  |
| 413      | 750                   | 6200                                 |   |  |                                     |
| 415      | 2.5                   | 990<br>1000*                         | 450<br>3500*                            | 26                                       | 18                                  |
| 416      | 12                    | 1200                                 | 3400                                    |  | 47                                  |
| 417      | 8                     | 2000                                 | 6000                                    | 33                                       | 22                                  |
| 418      | 2.2                   | 1050<br>2200*                        | 7800<br>1800*                           | 13                                       | 5.9                                 |
| 419      | 280                   | >8000                                |   |  |                                     |
| 420      | 1200                  | 8000<br>>8000*                       |   |  |                                     |
| 421      | 200                   | 4300<br>4600*                        |   |  |                                     |
| 422      | 50                    | 2200                                 | 1200                                    |  |                                     |
| 423      | 10                    | 2100<br>1800*                        | 1500                                    |  | 45                                  |
| 424      | 45                    | 2500                                 | 4000                                    |  |                                     |
| 425      | 0.8                   | 650<br>700*                          | 650                                     |  |                                     |
| 426      | 90                    | 4500<br>2500*                        |   |  |                                     |
| 427      | 180                   | 4500                                 |   |  | 36                                  |
| 428      | 280                   |                                      |   |  |                                     |
| 429      | 7000                  |                                      |   |  |                                     |
| 430      | 60                    | >8000                                |   |  |                                     |
| 431      | 8                     | >8000                                | 8000                                    |  |                                     |
| 432      | 1.6                   | 560                                  | 2000                                    |  |                                     |
| 433      | 2.9                   | 1000<br>1100*                        | 1100                                    |  |                                     |
| 434      | 4.9                   | 1600<br>1200*                        | 1800<br>1300*                           |  | 20                                  |
| 435      | 8                     | 4400                                 |   |  |                                     |
| 436      | 7.5                   | 2700                                 |   |  |                                     |
| 437      | 12                    | 1800                                 | 5000                                    |  |                                     |

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| Compound | UV-Visible<br>Ki (nM) | Cell<br>PBMC<br>avg.<br>IC50<br>(nM) | Whole<br>human<br>blood<br>IC50<br>(nM) | Clearance<br>Mouse,<br>i.v.<br>ml/min/kg | Clearance<br>Rat, i.v.<br>ml/min/kg |
|----------|-----------------------|--------------------------------------|---|--|-------------------------------------|
| 438      | 28                    | 1000                                 | 700<br>2900*                            |  | 22                                  |
| 439      | 3.7                   | 2800                                 | 3200<br>3400*                           |  |                                     |
| 440      | 2.3                   | 5000                                 | 2000                                    |  |                                     |
| 441      | 1                     | 2500                                 | 4500                                    |  |                                     |
| 442      | 3.2                   | 900                                  | 2000                                    |  | 54                                  |
| 443      | 3.6                   | 2800                                 | 1500                                    |  |                                     |
| 444      | 15                    | 3500                                 | 3500                                    |  |                                     |
| 445      | 135                   |                                      | 4000                                    |  |                                     |
| 446      | 62                    |                                      | 3000                                    |  |                                     |
| 447      | 5.8                   | 2500                                 | 1500                                    |  |                                     |
| 448      | 130                   |                                      | 4000                                    |  |                                     |
| 449      | 12                    | 1500                                 | 3200<br>13000*                          |  |                                     |
| 450      | 5                     | 800                                  | 2200<br>1700*                           | 18                                       | 12                                  |
| 451      | 4                     | 1800                                 | 1500<br>9000*                           |  |                                     |
| 452      | 4.5                   | 600<br>800*                          | 650<br>1600*                            |  | 27.3                                |
| 453      | 0.65                  | 1300                                 | 1900<br>1600*                           |  |                                     |
| 454      | 45                    | 2500                                 |   |  |                                     |
| 455      | 1.2                   | 400                                  | 2800<br>2600*                           |  | 54                                  |
| 456      | 4.5                   | 600<br>1300*                         | 600<br>1400*                            |  | 12.7                                |
| 457      | 6.2                   | 2000                                 | 3500                                    |  |                                     |
| 458      | 20                    | 2900                                 |   |  |                                     |
| 459      | 5                     | 1800                                 |   |  |                                     |
| 460      | 115                   | 400                                  | 2400                                    |  |                                     |
| 461      | 47                    |                                      |   |  |                                     |
| 462      | 40                    |                                      |   |  |                                     |
| 463      | 14                    | 2400<br>2800*                        |   |  |                                     |
| 464      | 2.5                   | 1000                                 | >1000<br>2500*                          |  |                                     |
| 465      | 3                     | 1000                                 | 800                                     |  |                                     |

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|    | Compound | UV-Visible<br>Ki (nM) | Cell<br>PBMC<br>avg.<br>IC50<br>(nM) | Whole<br>human<br>blood<br>IC50<br>(nM) | Clearance<br>Mouse,<br>i.v.<br>ml/min/kg | Clearance<br>Rat, i.v.<br>ml/min/kg |
|----|----------|-----------------------|--------------------------------------|---|--|-------------------------------------|
|    | 466      | 0.8                   | 1400                                 | 600                                     |  |                                     |
|    | 467      | 11                    | 1900                                 |   |  |                                     |
|    | 468      | 4.5                   | 850                                  | 2500                                    |  |                                     |
|    | 470      | 5                     | 500                                  | 360<br>500*                             |  | 63                                  |
| 5  | 471      | 1                     | 750                                  | 400                                     |  | 17                                  |
|    | 472      | 140                   |                                      |   |  |                                     |
|    | 473      | 1                     | 1000                                 | 400<br>450*                             |  |                                     |
|    | 474      | 85                    |                                      |   |  |                                     |
|    | 475      | 5.5                   | 690<br>650*                          | 400<br>350*                             | 31                                       | 21                                  |
| 10 | 476      | 7                     | 1600                                 | 2500                                    |  |                                     |
|    | 477      | 60                    |                                      |   |  |                                     |
|    | 478      | 380                   |                                      |   |  |                                     |
|    | 479      | 15                    | 900                                  | 700<br>2400*                            |  |                                     |
|    | 480      | 25                    | 2300                                 |   |  |                                     |
| 15 | 481      | 1.2                   | 390<br>930*                          | 600<br>500*                             |  | 34                                  |
|    | 482      | <0.2                  | 340                                  | 380<br>260*                             |  |                                     |
|    | 483      | 1.7                   | 900                                  | 700                                     |  |                                     |
|    | 484      | 2                     | 1550<br>1400*                        | 5000                                    |  | 15                                  |
|    | 485      | 2                     | 900                                  | 900                                     |  |                                     |
| 20 | 486      | 2.3                   | 480<br>570*                          | 500                                     |  | 37                                  |
|    | 487      | 2.4                   | 650<br>950*                          | 500<br>400*                             |  | 20                                  |
|    | 488      | 1.5                   | 940                                  | 750                                     |  |                                     |
|    | 489      | 6                     | 2250<br>1700*                        | 5000                                    |  |                                     |
|    | 490      | 4.3                   | 980<br>1000*                         | 700<br>1900*                            |  |                                     |
| 25 | 491      | 5                     | 2500                                 |   |  |                                     |
|    | 493      | 25                    | 1200                                 | 800<br>850*                             |  |                                     |

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|    | Compound | UV-Visible<br>Ki (nM) | Cell<br>PBMK<br>avg.<br>IC50<br>(nM) | Whole<br>human<br>blood<br>IC50<br>(nM) | Clearance<br>Mouse,<br>i.v.<br>ml/min/kg | Clearance<br>Rat, i.v.<br>ml/min/kg |
|----|----------|-----------------------|--------------------------------------|---|--|-------------------------------------|
|    | 494      | 15                    | 1350<br>1500*                        | 7000                                    |  |                                     |
|    | 495      | 43                    |                                      |   |  |                                     |
|    | 496      | 16                    | 1550<br>1600*                        | 6000                                    |  |                                     |
|    | 497      | 3.5                   | 740                                  | 350<br>700*                             |  |                                     |
| 5  | 498      | 1.5                   | 560                                  | 500<br>400*                             |  |                                     |
|    | 499      | 3.5                   | 1200<br>800*                         | 9000                                    |  |                                     |
|    | 605a     | 90                    | 2600                                 | >20000                                  |  |                                     |
|    | 605b     | 45                    | 10000                                |   | 97                                       |                                     |
|    | 605c     | 615                   | 4500                                 |   | 37                                       |                                     |
| 10 | 605d     | 95                    | 5100                                 | 16000<br>5100*                          | 33                                       |                                     |
|    | 605e     | 29                    | 2250                                 | >10000                                  |  | 24                                  |
|    | 605f     | 475                   | 12500                                |   |  |                                     |
|    | 605g     | 165                   | 22500                                |   |  |                                     |
|    | 605h     | 460                   | >25000                               |   |  |                                     |
| 15 | 605i     | 680                   | >20000                               |   |  |                                     |
|    | 605j     | 110                   | 8750                                 |   | 71                                       |                                     |
|    | 605m     | 650                   | 20000                                |   |  |                                     |
|    | 605n     | 12                    | 2100                                 | >20000                                  | 28                                       |                                     |
|    | 605o     | 72                    |                                      | 18000                                   |  |                                     |
| 20 | 605p     | 125                   | 3200                                 | >20000                                  |  |                                     |
|    | 605q     | 1000                  |                                      |   |  |                                     |
|    | 605s     | 150                   | 6000                                 |   |  |                                     |
|    | 605t     | 33                    |                                      |   |  |                                     |
|    | 609a     | 114                   | >30000                               |   |  |                                     |
| 25 | 609b     | 27                    | >20000                               |   |  |                                     |
|    | 619      | 300                   |                                      |   |  |                                     |
|    | 620      | 35                    | 1000                                 | 19000                                   |  |                                     |
|    | 621      | 7.2                   | 1300                                 | >20000                                  |  |                                     |
|    | 622      | 35                    | 1300                                 | >20000                                  |  |                                     |
| 30 | 623      | 9                     |                                      |   |  |                                     |
|    | 624      | 300                   |                                      |   |  |                                     |



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| Compound | UV-Visible<br>K <sub>i</sub> (nM) | Cell<br>PBMC<br>avg.<br>IC <sub>50</sub><br>(nM) | Whole<br>human<br>blood<br>IC <sub>50</sub><br>(nM) | Clearance<br>Mouse,<br>i.v.<br>ml/min/kg | Clearance<br>Rat, i.v.<br>ml/min/kg |
|----------|-----------------------------------|--|---|--|-------------------------------------|
| 625      | 105                               |  |   |  |                                     |
| 626      | 260                               |  |   |  |                                     |
| 627      | 43                                | 3250   | 8000  |  |                                     |
| 628      | 36                                | 2750   | >20000  |  |                                     |
| 629      | 230                               |  |   |  |                                     |
| 630      | 270                               |  |   |  |                                     |
| 631      | 805                               |  |   |  |                                     |
| 632      | 148                               |  |   |  |                                     |
| 633      | 92                                | 5750   | 20000   |  |                                     |
| 634      | 1400                              |  |   |  |                                     |
| 635      | 55                                | 1900<br>3400*                                    | 4000  |  |                                     |
| 605v     | 1100                              | >30000   |   |  |                                     |
| 2201     | 9                                 | 2000<br>3700*                                    | 3500  |  | 60                                  |
| 2100e    | 250                               | 800  | 600   |  |                                     |
| 2100a    | 100                               | 1100   | 850   |  |                                     |
| 2002     | 4                                 | 810<br>860*                                      | 70<br>1400*   |  | 32                                  |
| 2100d    | >100000                           | >20000   | >20000  |  |                                     |
| 2100c    | 7400                              | >20000   | >20000  |  |                                     |
| 2100b    | 8000                              | >20000   | >20000  |  |                                     |
| 2001     | 135                               | 1800   | 3500  |  |                                     |
| 1027     | 4000                              | >20000   | >20000  |  | 60                                  |
| 1015     | 40                                | 2500   | 1700  |  | 23                                  |

Table 6

| Compound | Fluorescent<br>Assay<br>k <sub>inact</sub><br>M <sup>-1</sup> s <sup>-1</sup> | Cell<br>PBMC<br>avg.<br>IC <sub>50</sub><br>(nM) | Whole<br>human<br>blood<br>IC <sub>50</sub><br>(nM) | Clearance<br>Mouse,<br>i.v.<br>ml/min/kg | Clearance<br>Rat, i.v.<br>ml/min/kg |
|----------|---|--|---|--|-------------------------------------|
| 108a     | 1x10 <sup>5</sup>   | 17500  |   |  |                                     |
| 136      | 5.4x10 <sup>5</sup>   | 870  | 2800  | 93                                       |                                     |

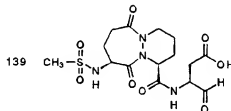
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| Compound | Fluorescent Assay<br>kinact<br>$M^{-1} s^{-1}$ | Cell<br>PBMC<br>avg.<br>IC50<br>(nM) | Whole<br>human<br>blood<br>IC50<br>(nM) | Clearance<br>Mouse,<br>i.v.<br>ml/min/kg | Clearance<br>Rat, i.v.<br>ml/min/kg |
|----------|--|--------------------------------------|---|--|-------------------------------------|
| 138      | $1.2 \times 10^5$                              | 900                                  | 2900                                    | 116                                      |                                     |
| 217d     | $4.7 \times 10^5$                              | 340                                  | 4000                                    |  |                                     |
| 280      | $4 \times 10^5$                                | 650                                  | >1000                                   |  | 187                                 |
| 283      | $1 \times 10^5$                                | <200                                 | 450                                     |  | 104                                 |
| 284      | $3.5 \times 10^5$                              | 470                                  | 550                                     | 77                                       | 100                                 |
| 285      | $4.3 \times 10^5$                              | 810                                  | 1000                                    | 130                                      | 50                                  |

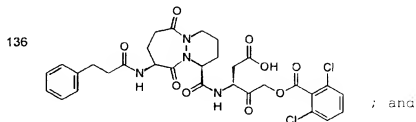
\* Values obtained upon reassay.

Example 10

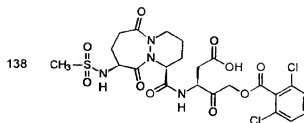
Compound 139 was synthesized by a method  
 10 similar to the method used to synthesize 47a.



Compounds 136 and 138 were synthesized by a  
 method similar to the method used to synthesize 57b.

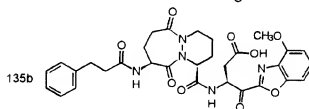
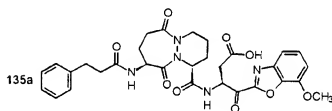


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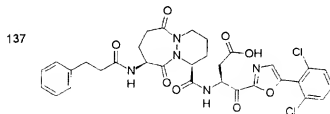


Compounds **135a**, **135b**, and **137** were synthesized by a method similar to the method used to synthesize **69a**.

5



; and



Compounds **813e**, **814c**, **814e**, **817c**, **817d**, **817e**, **820b**, **823b**, **823e**, **826e**, **827e**, **830e**, **832e**, **835e**, **838e**,  
 10 **846**, **857**, **865**, **902**, **904a**, **907a**, **907b**, **1004-1013**, **1015-**

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1045, 1046-1068, 1070-1091, and 1093-1099 were synthesized by methods similar to those used to synthesize compound 264 and the corresponding compounds in Examples 10 and 11.

- 5           Compounds 47a, 47b, 108a, 108b, 125b, 213e, 214c, 217c, 217d, 217e, 220b, 223b, 223e, 226e, 227e, 230e, 232e, 235e, 238e, 246, 257, 264, 265, 280-287, 302, 304a, 307a, and 307b were synthesized as described below.

- 10 H. N-(N-Acetyl-tyrosinyl-valinyl-pipecolyl)-3-amino-4-oxobutanoic acid.

Step A. N-(N-tert-Butoxycarbonylpipecolyl)-4-amino-5-benzyloxy-2-oxotetrahydrofuran.

- Reaction of N-tert-butoxycarbonylpipecolic  
15 acid (460 mg, 2.0 mmol) and N-allyloxycarbonyl-4-amino-5-benzyloxy-2-oxotetrahydrofuran (530 mg, 1.82 mmol) was carried out by a method analogous to that reported by Chapman (Bioorg. & Med. Chem. Lett. 2, pp. 613-618, (1992)) to give 654 mg of the title compound.

- 20           <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub> (existing as rotamers)) δ 7.35 (m, 5H), 6.88 (br. s, 1H), 4.9-4.45(m, 4H), 3.95+ (br. m, 2H), 3.06 (m, 1H), 2.9 (m, 1H), 2.7 (br. m, 1H), 2.45 (m, 1H), 2.2 (m, 1H), 1.7-1.5 (m, 3H), 1.45 (two s, 9H).

- 25           Step B. N-Pipecolyl-4-amino-5-benzyloxy-2-oxotetrahydrofuran.

N-(N-tert-Butoxycarbonylpipecolyl)-4-amino-5-benzyloxy-2-oxo-tetrahydrofuran (654 mg) was dissolved in 15 ml of 25% trifluoroacetic acid in dichloromethane

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and stirred at room temperature. The mixture was concentrated to give a gummy residue. The residue was dissolved in dichloromethane and washed with 10% sodium bicarbonate. The organic layer was dried over

- 5 anhydrous sodium sulfate, filtered, and concentrated to give 422 mg of the title compound as a beige solid.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.38 (m, 5H), 7.15 (d, 1H), 5.55 (d, 1H), 4.95-4.8 (m, 1H), 4.78 (m, 1H), 4.65 (d, 1H), 4.45 (m, 1H), 3.2 (m, 0.5H), 3.05 (m, 10 0.5H), 2.95 (m, 0.5H), 2.85 (m, 0.5H), 2.65 (m, 1H), 2.55-2.38 (m, 1H), 1.95 (m, 1H), 1.8 (m, 1H), 1.6 (m, 2H), 1.38 (m, 2H).

Step C. N-(N-Acetyl-tyrosinyl-valinyl-pipecolyl)-4-amino-5-benzoyloxy-2-oxo-tetrahydrofuran.

15

N-Acetyl-tyrosinyl-valine (464 mg, 1.44 mmol) and N-Pipecolyl-4-amino-5-benzoyloxy-2-oxotetrahydrofuran (412 mg, 1.3 mmol) were dissolved in 5 ml each of dimethylformamide and dichloromethane and  
20 cooled to 0°C. To the cooled solution was added 1-hydroxybenzotriazole (HOBT; 210 mg, 1.56 mmol) followed by the addition of 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC; 326 mg, 1.7 mmol). After stirring for 18 hours, the mixture was  
25 diluted with ethyl acetate and washed with water, 10% sodium hydrogen sulfate, 10% sodium bicarbonate, and water. The organic layer was concentrated to give a crude solid that was purified by flash chromatography ( $\text{SiO}_2$ ) eluting with 94:6:1

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(dichloromethane:isopropanol:pyridine) to give 370 mg of the title compound.

<sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD (existing as diastereomers as well as rotamers)) δ 7.35 (m, 5H),  
5 7.05 (m, 2H), 6.68 (m, 2H), 5.65 & 5.25 (m, 1H), 4.9-3.95 (m, 8H), 3.4-2.6 (m, 4H), 2.5-2.1 (m, 1H), 1.98 (s, 1H), 1.9 (s, 1H), 1.85 (s, 1H), 1.8-1.6 (m, 2H), 1.55-1.3 (m, 4H), 0.95-0.85 (m, 6H).

Step D. N-(N-Acetyl-tyrosinyl-valinyl-pipecolyl)-3-amino-4-oxobutanoic acid.  
10

To a solution of 100 mg of N-(N-Acetyl-tyrosinyl-valinyl-pipecolyl)-4-amino-5-benzyloxy-2-oxotetrahydrofuran in 10 ml of methanol was added 60 mg of Pd(OH)<sub>2</sub> on carbon and the mixture placed under an  
15 atmosphere of hydrogen via a balloon. The mixture was filtered through Celite and concentrated providing a white solid. This crude solid was dissolved in 2 ml of methanol and triturated with diethyl ether affording 26 mg of the title compound.

20 <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD(existing as diastereomers as well as rotamers)) δ 7.1 (m, 2H), 6.7 (m, 2H), 5.2 (br. m, 1H), 4.8-3.6 (m, 6H), 3.2-2.5 (m, 4H), 2.5-2.1 (m, 1H), 1.95 (three s, 3H), 1.9-1.3 (m, 6H), 1.1-0.7 (m, 6H).

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K. N-(N-Acetyl-tyrosinyl-valinyl-(4-benzyloxy)prolinyl)-3-amino-4-oxobutanoic acid.

Step A. N-(N-Allyloxycarbonyl-4-benzyloxyprolinyl)-3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone.

The title compound was prepared by the reaction of N-allyloxycarbonyl-4-benzyloxyproline and 3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone (T.L. Graybill et. al., Abstracts of papers, 206th National Meeting of the American Chemical Society, Abstract MEDI-235. Chicago, IL. (1993)) under similar peptide coupling conditions as reported above (compound H; Step C).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.05 (br. s, 1H), 7.85 (br. m, 1H), 7.4-7.2 (m, 5H), 7.15 (br. s, 1H), 6.55 (br. s, 1H), 5.9 (m, 1H), 5.1-4.9 (br. m, 2H), 4.65-4.4 (m, 4H), 4.2 (br. m, 1H), 3.75-3.5 (m, 2H), 2.75-2.55 (m, 2H), 2.5 (br. m, 1H), 2.25 (br. m, 1H) 1.4 (s, 9H).

Step B. N-(N-Acetyl-tyrosinyl-valinyl-(4-benzyloxyprolinyl))-3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone.

The title compound was prepared by reaction of N-acetyl-tyrosinyl-valine and N-(N-allyloxycarbonyl-4-benzyloxyprolinyl)-3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone by reaction conditions reported for compound H, step A.

$^1\text{H}$  NMR (500MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.35-7.2 (m, 6H), 7.0 (d, 2H), 6.65(d, 2H), 4.85 (m, 1H), 4.6-4.45 (m, 4H), 4.3 (br. m, 1H), 4.15 (m, 1H), 3.7 (m, 1H), 2.95 (m,

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1H), 2.75-2.6 (m, 3H), 2.35 (m, 1H), 2.1 (m, 1H), 1.9 (s, 3H), 1.4 (s, 9H), 0.95 (d, 3H), 0.90 (s, 3H).

Step C. N-(N-Acetyl-tyrosinyl-valinyl-(4-benzyloxyprolinyl))-3-amino-4-oxobutanoic acid.

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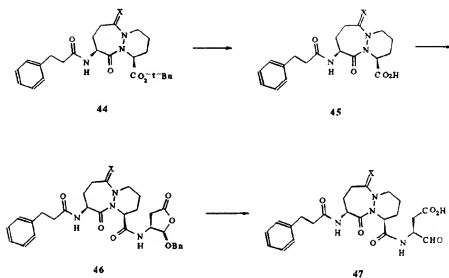
N-(N-Acetyl-tyrosinyl-valinyl-(4-benzyloxyprolinyl))-3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone (270 mg) was dissolved into 10 ml of 25% trifluoroacetic acid in dichloromethane and stirred at room temperature for 3 hours. The mixture was concentrated to give a solid residue. The residue was dissolved into a 10 ml mixture of methanol:acetic acid:37% formaldehyde (3:1:1) and stirred at room temperature for 1 hour. The mixture was concentrated and the resulting residue purified by flash chromatography (SiO<sub>2</sub>) eluting with dichloromethane/methanol/formic acid (100:5:0.5) to give 37 mg of the title compound.

<sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD (existing as a 1:1 mixture of diastereomers of the hemiacetal)) δ 7.4-7.25 (m, 5H), 7.0 (d, 2H), 6.65 (d, 2H), 4.65-4.05 (m, 7H), 3.75-3.4 (m, 2H), 3.05-2.3 (m, 5H), 2.2-1.95 (m, 2H), 1.90 (s, 3H), 1.0 (d, 3H), 0.95 (d, 3H).

20



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(a) X = O

(b) X = H<sub>2</sub>

(1*S*,9*S*) *t*-Butyl 6,10-dioxo-octahydro-9-(3-phenylpropionylamino)-6*H*-pyridazino[1,2-*a*]

- 5 [1,2]diazepine-1-carboxylate (**44a**). To a solution of (1*S*,9*S*)*t*-butyl 9-amino-6,10-dioxo-octahydro-6*H*-pyridazino [1,2-*a*][1,2]diazepine-1-carboxylate (690mg; 2.32mmol; GB 2128984) in dioxane (16ml) and water (4ml) at 0°C was added solid sodium bicarbonate (292mg; 3.48mmol) followed by dropwise addition of 3-phenylpropionyl chloride (470mg; 2.78mmol). The mixture was stirred at room temperature for 2h then more sodium bicarbonate (200mg; 2.38mmol) and 3-phenylpropionyl chloride (100mg; 0.6mmol) were added.
- 15 The mixture was stirred for a further 2h at room temperature, diluted with ethyl acetate (50ml), washed with saturated sodium bicarbonate (2 x 25ml) then dried (MgSO<sub>4</sub>) and concentrated. The residue was purified by flash chromatography (0-50% ethyl acetate/chloroform).

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- and finally crystallized by trituration with ether to afford 860mg (86%) of a white solid: mp. 137-138°C;  $[\alpha]_D^{23}$  -95.1° (c 0.549, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3327, 1736, 1677, 1664, 1536, 1422, 1156; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.24 (5H, m), 6.50 (1H, d, J=7.5), 5.24 (1H, m), 4.90 (1H, m), 4.60 (1H, m), 3.44 (1H, m), 2.93 (2H, m), 2.84 (1H, m), 2.64 (1H, m), 2.54 (2H, m), 2.26 (2H, m), 1.70 (4H, m), 1.70 (9H, s). MS(FAB, m/z): 430 (M<sup>+</sup> + 1), 374, 242, 105, 91.
- 10 (1S,9S) t-Butyl octahydro-10-oxo-9-(3-phenylpropionylamino)-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxylate (44b), was prepared from (1S,9S) t-butyl 9-amino-octahydro-10-oxo-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (Attwood et al., J. Chem. Soc. Perkin 1, pp. 1011-19 (1986)) as for 44a, to afford 810mg (81%) of a colorless oil:  $[\alpha]_D^{23}$  - 33.5° (c 0.545, CH<sub>2</sub>Cl<sub>2</sub>); IR (film) 3334, 2935, 1737, 1728, 1659, 1642; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.24 (5H, m), 6.75 (1H, d, J=6.7), 5.27 (1H, m), 4.92 (1H, m), 3.39 (1H, m), 3.03 (4H, m), 2.55 (3H, m), 2.33 (1H, m), 2.17 (1H, m), 1.80 (5H, m), 1.47 (9H, s), 1.39 (1H, m). MS(FAB, m/z): 416 (M<sup>+</sup> + 1), 360, 211, 143, 97.

- (1S,9S) 6,10-Dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid (45a). To a solution of (1S,9S) t-butyl 6,10-dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (44a) (800mg; 1.863mmol) in dry dichloromethane (5ml) at 0°C was added trifluoroacetic acid (5ml). The solution was stirred at room temperature for 3h then concentrated. Dry

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ether (10ml) was added to the residue then removed under vacuum. This process was repeated three times to afford a crystalline solid. The solid was triturated with ether and filtered to afford 590mg (85%) of a  
5 white crystalline solid: mp. 196-197.5°C;  $[\alpha]_D^{23}$  -129.5° (c 0.2, CH<sub>3</sub>OH); IR (KBr) 3237, 1729, 1688, 1660, 1633, 1574, 1432, 1285, 1205; <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  8.28 (1H, d, J=7.4), 7.22 (5H, m), 5.32 (1H, dd, J=5.9, 2.9), 4.75 (1H, m), 4.51 (1H, m), 3.50 (1H, m), 3.01 (1H, m), 2.91  
10 (2H, m), 2.55 (2H, m), 2.29 (3H, m), 1.95 (2H, m), 1.71 (2H, m). Anal. Calcd for C<sub>19</sub>H<sub>23</sub>N<sub>3</sub>O<sub>5</sub>: C, 61.12; H, 6.21; N, 11.25. Found: C, 60.80; H, 6.28; N, 10.97. MS(FAB, m/z) 374 (M<sup>+</sup> + 1), 242, 105, 91.

(1*S*,9*S*) Octahydro-10-oxo-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a]-[1,2]diazepine-1-carboxylic acid  
15 (45b), was prepared from (1*S*,9*S*) t-butyl octahydro-10-oxo-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a]-[1,2]diazepine-1-carboxylate (44b) by the method described for compound 45a to afford 657mg  
20 (96%) of 45b as a crystalline solid: mp. 198-202°C;  $[\alpha]_D^{23}$  -86.2° (c 0.5, CH<sub>3</sub>OH); IR (KBr) 3294, 2939, 1729, 1645, 1620, 1574, 1453, 1214; <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  7.92 (1H, d, J=7.9), 7.20 (5H, m), 5.29 (1H, m), 4.90 (1H, m), 3.47 (1H, m), 3.08 (2H, m), 2.90 (2H, m), 2.55 (3H, m), 2.36 (1H, m), 1.81 (5H, m), 1.43 (2H, m). MS(FAB,  
25 m/z) 360 (M<sup>+</sup> + 1), 211, 143, 91.

[3*S*,2*R*,*S*, (1*S*,9*S*)] N-(2-Benzoyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a]-[1,2]diazepine-1-carboxamide (46a).  
30 To a solution of (1*S*,9*S*) 6,10-dioxo-octahydro-9-(3-phenyl-propionylamino)-6H-pyridazino[1,2-a]

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[1,2]diazepine-1-carboxylic acid (**45a**) (662mg; 1.773mmol) in dry dichloromethane (9ml) and dry dimethyl formamide (3ml) at room temperature was added bis(triphenylphosphine)palladium chloride (30mg) and

5 (3*S*,2*R*,*S*)-3-allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydrofuran (Chapman, Bioorg. Med. Chem. Lett., 2, pp. 613-18 (1992)) (568mg; 1.95mmol) followed by dropwise addition of tri-*n*-butyltin hydride (1.19g; 4.09mmol). 1-Hydroxy-benzotriazole (479mg; 3.546mmol)

10 was added to the mixture and the mixture was cooled to 0°C before addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (408mg; 2.128mmol). The mixture was stirred at room temperature for 3.25h then diluted with ethyl acetate (50ml), washed twice

15 with dilute hydrochloric acid (20ml), twice with saturated sodium bicarbonate (20ml), once with brine then dried (MgSO<sub>4</sub>) and concentrated. The resulting oil was purified by flash chromatography (0-100% ethyl acetate/chloroform) to afford 810mg (81%) of **46a** as a

20 mixture of anomers: mp. 92-94°C; IR (KBr) 3311, 1791, 1659, 1651, 1536; <sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 7.49, 6.56 (1H, 2d, *J*=6.7, 7.8), 7.29 (10H, m), 6.37, 6.18 (1H, 2d, *J*=7.7, 7.6), 5.56, 5.34 (1H, d, s, *J*=5.2), 5.08-4.47 (6H), 3.18-2.80 (5H), 2.62-2.28 (5H), 2.04-1.53 (5H).

25 MS(FAB, *m/z*), 563 (*M*<sup>+</sup> + 1), 328, 149, 91.

[3*S*,2*R*,*S*, (1*S*,9*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-octahydro-10-oxo-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-*a*]

[1,2]diazepine-1-carboxamide (**46b**), was prepared from

30 **45b** by the method described for **46a** to yield 790mg (96%) of a glass: m.p. 58-60°C; IR (KBr) 3316, 2940, 1793, 1678, 1641, 1523, 1453, 1120; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ

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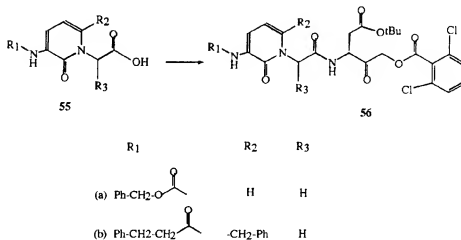
7.28 (1H, m), 6.52, 6.42 (1H, 2d,  $J=7.2$ , 7.1), 5.53, 5.44 (1H, d, s,  $J=5.2$ ), 5.35 (1H, m), 4.6-4.9, 4.34 (4H, m), 3.1-2.8 (6H, m), 2.6-2.1 (7H), 1.95-1.05 (5H). MS (FAB,  $m/z$ ), 549 ( $M^+ + 1$ ), 400, 310, 279, 91.

- 5 [3*S*(1*S*,9*S*)] 3-(6,10-Dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (47a). A mixture of [3*S*, 2*R*,*S*, (1*S*,9*S*)] N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (46a) (205mg; 0.364mmol), 10% palladium on carbon (200mg) and methanol (20ml) was stirred under hydrogen at atmospheric pressure for 5h. The mixture was filtered then concentrated to yield 15 154mg (90%) of a glass: mp. 116-118°C;  $[\alpha]_D^{23}$  -140° (c 0.1, CH<sub>3</sub>OH); IR (KBr) 3323 (br), 1783, 1731, 1658, 1539, 1455, 1425; <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  7.21 (5H, m), 5.17 (1H, m), 4.73 (1H, m), 4.50 (2H, m), 4.23 (1H, m), 3.38 (1H, m), 3.06 (1H, m), 2.91 (2H, m), 2.73-2.18 (6H, m) and 2.01-1.59 (5H, m). Anal. Calcd for C<sub>23</sub>H<sub>27</sub>N<sub>4</sub>O<sub>7</sub> + H<sub>2</sub>O : C, 56.32; H, 6.16; N, 11.42. Found: C, 56.29; H, 6.11; N, 11.25. MS (FAB,  $m/z$ ) 473 ( $M^+ + 1$ ), 176, 149, 105, 91.

- [3*S*(1*S*,9*S*)] 3-(Octahydro-10-oxo-9-(3-phenylpropionylamino)-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (47b), was prepared from 46b by the method described for 47a. The residue was purified by flash chromatography (0-10 methanol/chloroform) to afford 65mg (52%) of a glass; 30 m.p. 87-90°C;  $[\alpha]_D^{23}$  -167.0° (c 0.1, methanol); IR (KBr) 3329, 2936, 1786, 1727, 1637; <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$

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7.23 (5H, m), 5.29 (1H, m), 4.83 (1H, m), 4.59 (1H, d,  $J=3.6$ ), 4.29 (1H, m), 3.3-3.0 (3H, m), 2.91 (2H, m), 2.70-2.34 (5H, m), 2.19 (2H, m), 1.75 (4H, m), 1.36 (2H, m). Anal. Calcd for  $C_{23}H_{30}N_4O_6 + 0.5H_2O$ : C, 59.09; H, 6.68; N, 11.98. Found: C, 58.97; 6.68; N, 11.73. MS (FAB,  $m/z$ ) 459 ( $M^+ + 1$ ), 310, 149, 105, 91.



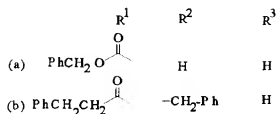
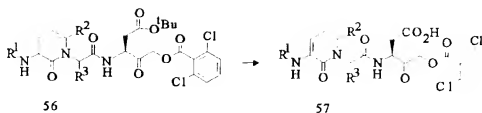
t-Butyl N-2-(3-benzyloxycarbonylamino-1,2-dihydro-2-oxo-1-pyridyl)acetyl-3-amino-5-(2,6-dichlorobenzoyloxy)-4-oxo-pentanoate (56a). The acetic acid (55a) (WO 93 21213) in THF (2ml) was stirred at room temperature and treated with 1-hydroxybenzotriazole (60mg, 0.448mmol) and dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (47mg, 0.246mmol). After 5 mins water (2 drops) was added and stirring continued for 20 minutes. Bis(triphenylphosphine) palladium II chloride (6mg) was added followed by a solution of t-butyl 3-(allyloxycarbonylamino)-4-oxo-5-(2,6-dichlorobenzoyl-oxy)pentanoate (WO 93 16710) (103mg, 0.224mmol) in THF (1ml). Tributyltin hydride

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(0.09ml, 0.336mmol) was added dropwise over 1 hour at room temperature. The mixture was stirred for a further 3 hours and poured onto ethyl acetate, washed with 1M HCl, aqueous NaHCO<sub>3</sub>, brine, dried over MgSO<sub>4</sub>,  
5 and concentrated *in vacuo*. The residue was triturated with pentane and the supernatant discarded. The remaining solid was purified by flash chromatography (50% ethyl acetate/hexane) to afford the title compound 92mg (63%) as a colorless oil:  $[\alpha]_D^{26}$  -29.6° (c 1.1,  
10 CH<sub>2</sub>Cl<sub>2</sub>); IR (film) 3377, 3365, 3332, 3312, 1733, 1691, 1650, 1599, 1515, 1366, 1261, 1153, 1068, 747; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.09 (1H, d, J = 6.8), 7.84 (1H, s), 7.58 (1H, d, J = 8.3), 7.33 (8H, m), 7.02 (1H, dd, J = 6.9, 1.7), 6.33 (1H, t, J = 7.2), 5.20 (2H, s), 5.12 (2H,  
15 m), 4.89 (1H, dt), 4.65 (2H, m), 2.80 (2H, m), 1.38 (9H, s).

**t-Butyl N-2-(6-benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl)acetyl-3-amino-5-(2,6-dichlorobenzoyloxy)-4-oxo-pentanoate (56b)**, was prepared  
20 by the method described for (56a) which afforded the title compound (66%) as a colorless oil: IR (film) 3364, 3313, 1738, 1688, 1648, 1600, 1566, 1514, 1433, 1369, 1254, 1152; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.40 (1H, d, J 7.6), 8.30 (1H, s), 7.28 (13H, m), 6.20 (1H, d, J = 7.6),  
25 5.12 (2H, q), 4.86 (1H, m), 4.65 (2H, q), 4.06 (2H, s), 3.07-2.61 (6H, m), 1.39 (9H, s).

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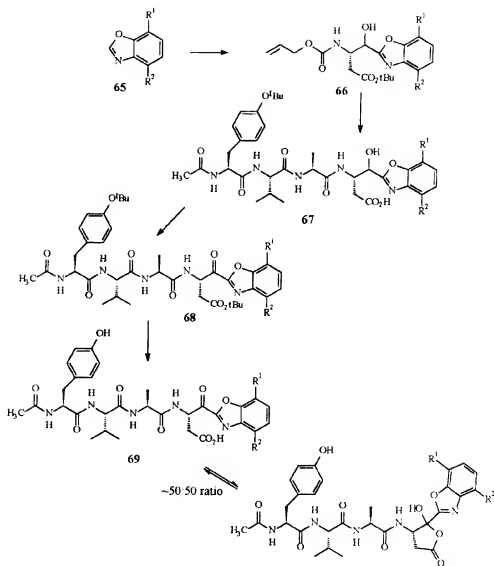


N-2(3-Benzyloxycarbonylamino-1,2-dihydro-2-oxo-1-pyridyl)acetyl-3-amino-5-(2,6-dichlorobenzoyloxy)-4-oxo-pentanoic acid (57a; Q). The ester 56a (210mg, 0.356mmol) in dichloromethane (0.5ml) was cooled to 0°C and treated with trifluoroacetic acid (0.5ml), stirred and warmed to 20°C over 30 minutes. The solution was evaporated to dryness under reduced pressure, redissolved in dichloromethane and concentrated (x3). The residue was triturated with ethyl acetate and diluted with ether to afford the title compound 162mg (85%) as a colorless solid: m.p. 165-8°C (decomposition);  $[\alpha]_D^{23}$  -38.8° (c 0.1, CH<sub>3</sub>OH); IR (KBr) 3332, 3275, 1723, 1658, 1649, 1597, 1581, 1562, 1526, 1432, 1385, 1258, 1218, 1206; <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ 8.96 (1H, d, J = 7.3), 8.34 (1H, s), 7.85 (1H, dd, J = 7.3), 7.58 (3H, m), 7.35 (5H, m), 6.29 (1H, t, J = 7.3), 5.26 (2H, m), 5.15 (2H, s), 4.69 (3H, m), 2.75 (2H, m). Anal. Calcd. C<sub>27</sub>H<sub>23</sub>N<sub>3</sub>O<sub>9</sub>Cl<sub>2</sub>: C, 53.66; H, 3.84; N, 6.95. Found: C, 53.36; H, 3.90; N, 6.81. M.S. (+ FAB; 604 (M<sup>+</sup> + 1), 285, 241, 195, 173, 149, 91.



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N-2-(6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl) amino-1-pyridyl)acetyl-3-amino-5-(2,6-dichloro-benzoyloxy)-4-oxo-pentanoic acid (57b; **2**), was prepared by the method described for 57a which afforded the  
5 title compound (78%) as colorless crystals: m.p. 116-120°C (decomposition);  $[\alpha]_D^{26}$  -41.1° (c 0.1, CH<sub>3</sub>OH); IR (KBr) 3299, 1739, 1715, 1689, 1666, 1645, 1598, 1563, 1518, 1432, 1209, 1151; <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ 9.24 (1H, s), 8.88 (1H, d, J = 7.6), 8.18 (1H, d, J = 7.7), 7.60  
10 (3H, m), 7.26 (10H, m), 6.06 (1H, d, J = 7.7), 5.23 (2H, ABq), 4.69 (3H, m), 3.93 (2H, s), 2.78 (6H, m).  
Anal. Calcd. for C<sub>35</sub>H<sub>31</sub>N<sub>3</sub>O<sub>8</sub>Cl<sub>2</sub> · H<sub>2</sub>O: C, 59.16; H, 4.68; N, 5.91. Found: C, 59.38; H, 4.53; N, 5.84. M.S. (+ FAB); 694, (Cl=35, 37), (M<sup>+</sup> + 1); 692 (Cl=35, 35), (M<sup>+</sup>  
15 + 1).



(a)  $R^1 = \text{OCH}_3$ ,  $R^2 = \text{H}$

(b)  $R^1 = H, R^2 = OCH_3$

7-Methoxybenzoxazole (65a). A mixture of 2-nitro-6-methoxyphenol (2.62g, 15.5mmol) (EP 333176) and 10% 5 Palladium on carbon (130mg) in ethanol (50.0ml) was stirred under an atmosphere of H<sub>2</sub> for 75min. The

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mixture was filtered through Celite® then immediately treated with *p*-toluenesulphonic acid (32.0mg) and triethylorthoformate (6.45ml, 38.8mmol) then heated under reflux under an atmosphere of N<sub>2</sub>. After 20h *p*-toluenesulphonic acid (30.0mg) and triethylorthoformate (6.45ml, 38.8mmol) were added. After a total of 44h heating, the reaction was allowed to cool and reduced *in vacuo*. The resulting residue was purified by flash chromatography (25:75 ethyl acetate/hexane) to give 1.97g (85%) of the title compound as a yellow solid; m.p. 28-31°C; IR (film) 1629, 1497, 1434, 1285, 1097; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.09 (1H, s), 7.40 (1H, d, *J* = 8.0), 7.28 (1H, t, *J* = 8.0), 6.89 (1H, d, *J* = 8.0), 4.02 (3H, s); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 152.84, 145.82, 142.50, 139.99, 125.75, 113.42, 108.80, 56.97. Anal. Calcd. for C<sub>8</sub>H<sub>7</sub>N<sub>3</sub>O<sub>2</sub> · 0.1H<sub>2</sub>O: C, 63.65; H, 4.81; N, 9.29. Found: C, 63.43, H, 4.88, N, 9.05. M.S. (+ FAB); 150 (M<sup>+</sup> + 1).

**4-Methoxybenzoxazole (65b).** To a suspension of 4-hydroxybenzoxazole (2.00g, 14.8mmol) (Musser et al., Med. Chem., 30, pp. 62-67 (1987)) in acetone (80.0ml) was added dried K<sub>2</sub>CO<sub>3</sub> (2.25g, 16.3mmol) followed by iodomethane (1.38ml, 22.2mmol). The reaction was heated under reflux under N<sub>2</sub> for 4.5h, then filtered and reduced *in vacuo* to afford the crude product. The resulting residue was purified by flash chromatography (25:75 ethyl acetate/hexane) to give 2.0g (91%) of the title compound as a white crystalline solid: m.p. 72-74°C; IR (KBr) 3089, 1619, 1610, 1503, 1496, 1322, 1275, 1090, 1071, 780, 741; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.02 (1H, s), 7.32 (1H, t, *J* = 8.0), 7.18 (1H, d, *J* = 8.0), 6.81 (1H, d, *J* = 8.0), 4.04 (3H, s). Anal. Calcd. for

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$C_8H_7NO_2$ : C, 64.42; H, 4.73; N, 9.39. Found: C, 64.40; H, 4.84; N, 9.31;  $m/z$  (EI) 149 ( $M^+ + 1$ , 100%).

(3*S*, 4*R*,*S*) *t*-Butyl *N*-(allyloxycarbonyl)-3-amino-4-hydroxy-4-(2-(7-methoxybenzoxazolyl))butanoate (66a).

- 5 To a stirred solution of 7-methoxybenzoxazole 65a (548.6mg, 3.68mmol) in anhydrous THF (18.5ml) at  $-78^\circ\text{C}$  under  $N_2$  was added 1.56M *n*-butyl lithium in hexanes (2.47ml, 3.86mmol) dropwise, to produce a yellow colored solution. After stirring at  $-78^\circ\text{C}$  for 20 min,
- 10 dry  $MgBr_2OEt_2$  (1.045g, 4.05mmol) was added as a solid. The resulting heterogeneous mixture was warmed to  $-45^\circ\text{C}$  and stirred for 15min. The reaction mixture was then recooled to  $-78^\circ\text{C}$  and a solution of (S)-Alloc-Asp(*t*-Bu)H (946.4mg, 3.68mmol) in THF (18.5ml) was added
- 15 dropwise. The reaction was stirred at  $-78^\circ\text{C}$  for 30min, warmed to  $0^\circ\text{C}$  and stirred for 1h. The resulting homogeneous reaction was warmed to room temperature and stirred for 16h. The reaction was quenched with 5% sodium bicarbonate (3.5ml) then THF was removed *in*
- 20 *vacuo*. The resulting aqueous residue was extracted with methylene chloride (x6). The combined extracts were washed with brine, dried ( $MgSO_4$ ), filtered and reduced *in vacuo* to give 1.8g of crude product. Flash chromatography (40:60 ethyl acetate/hexane) gave 1.21g
- 25 (81%) of the title compound, an oil, as a mixture of diastereoisomers at C-4: IR ( $CH_2Cl_2$ ) 3425, 2983, 1725, 1504, 1290, 1157, 1101;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.35-7.19 (2: m), 6.89-6.81 (1H, m), 6.00-5.57 (2H, m), 5.32-5.05 (3H, m), 4.68-4.35 (3H, m), 4.01 (3H, s), 2.66-2.59 (2H, m), 1.45 (9H, s), 1.41 (9H, s);  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$
- 30 171.18, 171.09, 165.80, 165.30, 156.71, 156.60, 145.65, 142.76, 142.71, 140.82, 140.72, 133.23, 125.81, 125.72,

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118.41, 118.21, 113.07, 112.87, 108.95, 82.16, 70.28, 69.98, 66.52, 66.39, 57.03, 52.57, 52.29, 37.83, 36.86, 28.65. Anal. Calcd. for  $C_{20}H_{26}N_2O_7$ .  $0.6H_2O$ : C, 57.57; H, 6.57; N, 6.72. Found: C, 57.49, H, 6.34, N, 6.60.  
5 M.S. (+ FAB); 407 ( $M^+ + 1$ ); 351, 307, 154.

(3*S*, 4*R*,*S*) *t*-Butyl *N*-(allyloxycarbonyl)-3-amino-4-hydroxy-4-(2-(4-methoxybenzoxazolyl))butanoate (66*b*), was prepared according to the method described for 66*a* which afforded 1.29g (26%, 68% based on recovered  
10 starting material) of the title compound as an oil and as a mixture of diastereoisomers at C-4: IR ( $CH_2Cl_2$ ) 3400, 1725, 1625, 1505, 1369, 1354, 1281, 1263, 1226, 1158, 1092, 1048;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.34-7.24 (1*H*, *m*), 7.16 (1*H*, *d*, *J* = 8.2), 6.79 (1*H*, *d*, *J* = 7.9), 6.00-5.50  
15 (2*H*, *m*), 5.30-5.05 (3*H*, *m*), 4.70-4.35 (4*H*, *m*), 4.02 (3*H*, *s*), 2.90-2.45 (2*H*, *m*), 1.45-1.41 (9*H*, 2 *x s*). Anal. Calcd. for  $C_{20}H_{26}N_2O_7$ .  $0.4H_2O$ : C, 58.07; H, 6.53; N, 6.77. Found: C, 58.09; H, 6.41; N, 6.63. M.S. (+ FAB); 407 ( $M^+ + 1$ , 88%); 351 (100).

20 (3*S*, 4*R*,*S*) *t*-Butyl *N*-(*N*-acetyl-(*S*)-(O-*tert*-butyl-tyrosinyl)-(*S*)-valinyl-(*S*)-alaninyl)-3-amino-4-hydroxy-4-(2-(7-methoxybenzoxazolyl))butanoate (67*a*). To a stirred solution of the benzoxazole 66*a* (481.9mg, 1.19mmol) and Ac-Tyr(<sup>*t*</sup>Bu)-Val-Ala-OH (586.3mg, 1.30mmol) in methylene chloride (3.5ml) and DMF (3.5ml)  
25 was added bis(triphenylphosphine) palladium (II) chloride (18.0mg), followed by tributyltinhydride (0.80ml, 2.96mmol) dropwise. Hydroxybenzotriazole (320.4mg, 2.37mmol) was added and the mixture cooled to  
30 0°C. 1-Ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (278.2mg, 1.42mmol) was added and the

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mixture was allowed to warm to room temperature and stirred for 16.5h. The reaction was diluted with ethyl acetate and washed twice with 1M sodium hydrogensulphate, twice with saturated sodium bicarbonate, water, and brine. The organic layer was dried ( $\text{MgSO}_4$ ), filtered and reduced in vacuo to yield 2.0g of crude product. Flash chromatography (95:5 methylene chloride/methanol) gave 844.0mg (94%) of the title compound as a white solid: m.p. 205°C; IR (KBr) 3399, 3304, 2977, 1729, 1643, 1506, 1367, 1290, 1161;  $^1\text{H}$  NMR ( $d_6$ -DMSO)  $\delta$  8.24-7.78 (4H, m), 7.43-7.32 (2H, m), 7.23 (2H, d,  $J = 8.5$ ), 7.16-7.07 (1H, m), 6.93 (2H, d,  $J = 8.5$ ), 6.52, 6.40 (1H, 2 x d,  $J = 5.5$ ,  $J = 5.0$ ), 5.03, 4.78-4.49, 4.45-4.16 (5H, brt, 2 x m), 4.05, 4.04 (3H, 2 x s), 3.08-2.35 (14H, m), 2.11-1.89 (1H, m), 1.83 (3H, s), 1.49-1.32, 1.15, 1.0-0.81 (27H, s, 2 x m,  $J = 7.0$ );  $^{13}\text{C}$  NMR ( $d_6$ -DMSO)  $\delta$  175.55, 175.18, 173.88, 173.75, 173.05, 169.23, 157.28, 148.55, 146.16, 143.21, 136.63, 133.55, 128.87, 127.17, 115.78, 111.92, 84.02, 81.50, 71.40, 61.15, 60.05, 57.79, 53.39, 51.62, 43.76, 40.52, 34.58, 32.52, 31.60, 26.35, 23.11, 22.71, 21.76. Anal. Calcd. for  $\text{C}_{39}\text{H}_{55}\text{N}_5\text{O}_{10}$ .  $0.5\text{H}_2\text{O}$ : C, 61.40; H, 7.40; N, 9.18. Found: C, 61.43; H, 7.31; N, 9.07. M.S. (+ FAB); 754 ( $\text{M}^+ + 1$ ); 698, 338, 267.

(3S, 4R,S) t-Butyl N-(N-acetyl-(S)-(O-tert-butyl-tyrosinyl)-(S)-valinyl-(S)-alaninyl)-3-amino-4-hydroxy-4-(2-(4-methoxybenzoxazolyl))butanoate (67b), was prepared according to the method described for 67a which afforded 1.05g (94%) of the title compound as a fine white powder: m.p. 210-213°C (dec); IR (KBr) 3284, 2977, 1736, 1691, 1632, 1536, 1505, 1452, 1392, 1367, 1258, 1236, 1161, 1091;  $^1\text{H}$  NMR ( $d_6$ -DMSC)  $\delta$  8.20-

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- 7.75 (4H, m), 7.40-7.10 (4H, m), 7.00-6.80 (3H, m), 6.45, 6.34 (1H, 2 x d,  $J = 5.3$ ,  $J = 5.0$ ), 5.00-4.10 (5H, m), 4.00, 3.99 (3H, 2 x s), 3.00-2.25 (4H, m), 1.95 (1H, m), 1.78 (3H, s), 1.39-0.80 (27H, m). Anal.
- 5 Calcd. for  $C_{39}H_{55}N_5O_{10}$ .  $0.5H_2O$ : C, 61.40; H, 7.40; N, 9.18. Found: C, 61.58; H, 7.38; N, 8.91. M.S. (+ FAB); 754 ( $M^+ + 1$ , 30%); 72 (100).

- (3S) t-Butyl N-(N-acetyl-(S)-(O-tert-butyl-tyrosinyl)-(S)-valinyl-(S)-alaninyl)-3-amino-4-(2-(7-methoxybenzoxazolyl))-4-oxobutanoate (68a). The Dess-Martin reagent (1.082g, 2.55mmol) (Ireland et al., J. Org. Chem., 58, p. 2899 (1993); Dess et al., J. Org. Chem., 48, pp. 4155-4156 (1983)) was added to a stirred suspension of the alcohol **67a** (641.0mg, 0.85mmol) in
- 15 methylene chloride (46.0ml). The resulting mixture was stirred for 1h before being partitioned between saturated sodium thiosulphate: saturated sodium bicarbonate (1:1, 86.0ml) and ethyl acetate (86.0ml). The resultant organic phase was washed in turn with
- 20 saturated sodium thiosulphate: saturated sodium bicarbonate (1:1), saturated sodium bicarbonate, and brine. The organic phase was dried ( $MgSO_4$ ), filtered and reduced in vacuo to give 660.0mg of crude product. Flash chromatography (94:6 methylene chloride/methanol)
- 25 gave 636.0mg (100%) of the title compound as a white solid: m.p. 209°C;  $[\alpha]_D^{24} -21.8^\circ$  (c 0.16, methanol); IR (KBr) 3395, 3294, 2977, 1722, 1641, 1535, 1505, 1161;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  8.43-8.16 (1H, m), 7.97-7.62 (2H, m), 7.49-7.14 (3H, m), 7.08-6.95 (3H, m), 6.89-6.73 (2H, m), 5.81-5.68 (1H, m), 5.16-4.86 (2H, m), 4.53 (1H, brt), 4.03 (3H, s), 3.16-2.84 (4H, m), 2.11-1.84 (4H, m), 1.46-1.14 (21H, m), 0.92-0.78 (6H, m);  $^{13}C$  NMR

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(CDCl<sub>3</sub>)  $\delta$  186.28, 173.39, 171.90, 171.19, 171.03, 169.89, 156.43, 154.75, 146.32, 142.88, 140.98, 132.31, 130.54, 126.98, 124.73, 114.95, 111.42, 82.44, 78.71, 58.92, 57.20, 54.91, 53.47, 48.77, 39.43, 38.15, 32.79, 29.44, 28.60, 23.55, 20.27, 19.70, 19.34. M.S. (+ FAB); 752 (M<sup>+</sup> + 1); 696, 336, 265.

(3S) t-Butyl N-(N-acetyl-(S)-(O)-tert-butyl-tyrosinyl)-(S)-valinyl-(S)-alaninyl)-3-amino-4-(2-(4-methoxybenzoxazolyl))-4-oxobutanoate (68b), was prepared according to the method described for the ketone 68a which afforded 420mg (55%) of the title compound as a white solid: m.p. 211-213°C (dec); [ $\alpha$ ]<sub>D</sub><sup>24</sup> -23.9° (c 0.82, methanol); IR (KBr) 3277, 3075, 1723, 1690, 1632, 1530, 1506, 1392, 1366, 1269, 1234, 1160, 1094; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  8.15 (1H, brs), 7.7 (2H, brs), 7.46 (1H, t, J = 8.3), 7.24 (2H, d, J = 8.3), 7.10 (1H, brs), 7.03 (2H, d, J = 8.3), 6.83 (3H, m), 5.74 (1H, q, J = 6.9), 5.00 (2H, m), 4.51 (1H, t, J = 7.0), 4.07 (3H, s), 3.20-2.95 (4H, m), 2.00 (4H, m), 1.42 (3H, d, J = 6.8), 1.35 (9H, s), 1.23 (9H, s), 0.86 (6H, d, J = 6.7). M.S. (+ FAB); 752 (M<sup>+</sup> + 1, 7%); 72 (100).

(3S) N-(N-Acetyl-(S)-tyrosinyl-(S)-valinyl-(S)-alaninyl)-3-amino-4-(2-(7-methoxybenzoxazolyl))-4-oxobutanoate (69a; R). A solution of the ester 68a (600.0mg, 0.80mmol) in a 1:1 mixture of methylene chloride and trifluoroacetic acid (65.0ml) was stirred for 1h under a dry atmosphere of N<sub>2</sub>. The solution was then reduced in vacuo, taken up in ether and reduced again. This process was repeated six times to afford the crude product as an off white solid. Flash chromatography (gradient 95:5 to 80:20 methylene



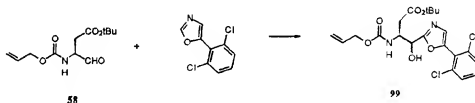
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chloride/methanol) gave 420.8mg (83%) of the title compound as a hygroscopic white solid. The product existed as a mixture of three isomers in CD<sub>3</sub>OD, consisting of the keto form (c 50%), and its acycloxy keto form (two isomers at C-4, c 50%): m.p. decomposes above 150°C;  $[\alpha]_D^{24}$  -33.2° (c 0.17, methanol); IR (KBr) 3300, 1715, 1658, 1650, 1531, 1517, 1204; <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  7.46-7.19 (2H, m), 7.16-6.91 (3H, m), 6.70-6.59 (2H, m), 5.62-5.49 (1H, m), 5.00-4.72 (1H, obscured m), 4.69-4.51 (1H, m), 4.49-4.08 (2H, m), 4.05-3.89 (3H, m), 3.16-2.47 (4H, m), 2.05-1.78 (4H, m), 1.41-1.11, 1.05-0.70 (9H, 2 x m). Anal. Calcd. for C<sub>31</sub>H<sub>37</sub>N<sub>5</sub>O<sub>10</sub>. 3H<sub>2</sub>O: C, 53.67; H, 6.25; N, 10.10. Found: C, 53.76; H, 5.56; N, 10.28. M.S. (+ FAB); 640 (M<sup>+</sup> + 1); 435, 147.

**(3S) t-Butyl N-(N-acetyl-(S)-tyrosinyl-(S)-valinyl-(S)-alaninyl)-3-amino-4-(2-(4-methoxybenzoxazolyl))-4-oxobutanoate (69b; 5)**, was prepared according to the method described for the acid **69a** which afforded the hygroscopic title compound 252mg (96%). The product existed as a mixture of three isomers in CD<sub>3</sub>OD, consisting of the keto form, and its acycloxy ketal form (two isomers at C-4). The product existed as a single isomer in d-6 DMSO: m.p. 200-203°C (dec.);  $[\alpha]_D^{24}$  -38.0° (c 0.23, methanol); IR (KBr) 3289, 2968, 1718, 1713, 1658, 1634, 1548, 1517, 1506, 1461, 1453, 1393, 1369, 1268, 1228, 1174, 1092; <sup>1</sup>H NMR (d<sub>6</sub>-DMSO)  $\delta$  9.20 (1H, brs), 8.71 (1H, d, *J* = 6.2), 8.10 (2H, m), 7.83 (1H, d, *J* = 8.7), 7.61 (1H, t, *J* = 8.2), 7.46 (1H, d, *J* = 8.2), 7.08 (3H, m), 6.65 (2H, d, *J* = 8.3), 5.50 (1H, q, *J* = 6.5), 4.50 (1H, m), 4.37 (1H, m), 4.20 (1H, m), 4.05 (3H, s), 3.09-2.77 (4H, m), 1.94 (1H, m), 1.79

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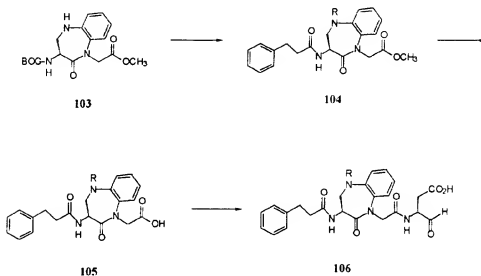
(3H, s), 1.23 (3H, d,  $J = 7.0$ ), 0.82 (6H, m). Anal. Calcd. for  $C_{31}H_{37}N_5O_{10}$ .  $1.5H_2O$ : C, 55.85; H, 6.05; N, 10.51. Found: C, 55.21; H, 5.69; N, 10.13. M.S. (+ FAB); 640 ( $M^+ + 1$ , 22%); 107 (100).



- 5 **3(S)-(Allyloxycarbonyl)-amino-4-[(2,6-dichloro-phenyl)-oxazol-2-yl]-4(R,S)-hydroxy-butyric acid tert-butyl ester (99)**. A solution of 5-(2,6-Dichlorophenyl)oxazole (2.71g, 12.7mmol; prepared by a similar method described in Tet. Lett. 23, p. 2369
- 10 (1972)) in tetrahydrofuran (65mL) was cooled to -78 °C under a nitrogen atmosphere. To this solution was added n-butyl lithium (1.5M solution in hexanes, 8.5mL, 13.3mmol) and stirred at -78 °C for 30min. Magnesium bromide etherate (3.6g, 13.9mmol) was added and the
- 15 solution was allowed to warm to -45 °C for 15min. The reaction was cooled to -78 °C and aldehyde **58** (3.26g, 12.7mmol; Graybill et al., Int. J. Protein Res., 44, pp. 173-182 (1993)) in tetrahydrofuran (65mL) was added dropwise. The reaction was stirred for 25min., then
- 20 allowed to warm to -40 °C and stirred for 3h, and then at room temperature for 1h. The reaction was quenched with 5%  $NaHCO_3$  (12mL) and stirred for 3h. The tetrahydrofuran was removed in vacuo and the resulting residue was extracted with dichloromethane. The
- 25 organic layer was washed with saturated sodium chloride solution and dried over magnesium sulfate, filtered, and concentrated to yield 6.14g of the title compound.

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Purification gave 4.79g (80%) of **99**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.45(s, 9H), 2.7-2.5(m, 2H), 2.8(dd, 1H), 4.2, 4.4(2 x d, 1H), 4.7-4.5(m, 3H), 5.35-5.1(m, 2H), 5.6, 5.7(2 x d, 1H), 6.0-5.8(m, 1H), 7.2(d, 1H), 7.3(m, 1H), 7.4(m, 2H).



a R = H

b R =  $\text{COCH}_2\text{CH}_2\text{Ph}$ c R =  $\text{CH}_2\text{Ph}$ 

[2-Oxo-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-yl]acetic acid methyl ester (**104a**). Anhydrous hydrogen chloride was bubbled into a solution of (3(S)-tert-butoxycarbonylamino-2-oxo-2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-yl)acetic acid methyl ester (**103**, 1g, 2.86 mmol) in 25 ml of ethyl acetate for 2 minutes then stirred for 1 hour at room temperature. The reaction was evaporated to give 2-oxo-3(S)-amino-2,3,4,5-

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tetrahydrobenzo[b][1,4]diazepin-1-yl acetic acid methyl ester hydrochloride as a white solid.

The hydrochloride salt and hydrocinnamic acid (0.47 g, 3.15 mmol) were dissolved into 20 ml of

5 dimethylformamide and cooled to 0 °C.

Diisopropylethylamine (1 ml, 5.72 mmol) was added to the solution followed by the addition of N-hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. After stirring for 18

10 hours at room temperature, the mixture was diluted with 150 ml of ethyl acetate and washed with 10% sodium hydrogen sulfate, 10% sodium bicarbonate, and brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated to a crude solid that

15 was purified by flash chromatography eluting with 7:3 ethyl acetate/dichloromethane to afford 600 mg (55%) of the title compound as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.3-6.85 (9H, m), 6.55-6.0 (1H, d), 4.88-4.82 (1H, m), 4.72-4.65 (1H, d), 4.28-4.22 (1H, m), 3.95-3.9 (1H, m),

20 3.78 (3H, s), 3.65 (1H, br. s), 3.28-3.2 (1H, m), 2.95-2.84 (2H, m), 2.55-2.4 (2H, m).

**(3(S)-(3-Phenylpropionylamino)-2-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl)acetic acid (105a).**

(3(S)-(3-Phenylpropionylamino)-2-oxo-2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-yl)acetic acid

25 methyl ester (104a) was dissolved in 90% methanol. Lithium hydroxide hydrate was added to the reaction and the reaction was stirred at room temperature for 4 h. The reaction was evaporated in vacuo to give a white

30 solid. This was dissolved in 20 ml of water and acidified to pH 5 and extracted with ethyl acetate to afford 304 mg (88%) of the title compound as a white

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solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.5-6.9 (11H, m), 4.92-4.8 (1H, m), 4.7-4.58 (1H, d), 4.38-4.25 (1H, d), 3.88-3.78 (1H, m), 3.45-3.25 (1H, m), 3.05-2.85 (2H, m), 2.55-2.45 (2H, m).

- 5 4-Oxo-3(S)-[2-[2-oxo-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-ylacetylaminobutyric acid (106a). N-[1-(2-Benzyloxy-5-oxotetrahydrofuran-3-ylcarbamoyl-methyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-3-phenylpropionamide was prepared from 105a by the  
10 procedure used to prepare compound H (stepA) to afford 390 mg (93%) of the product as diastereomers. <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.58-7.22 (14H, m), 5.78-5.73 (0.5 H, d), 5.64 (0.5 H, s), 5.0-4.72 (4H, m), 4.54-4.42 (2H, m), 3.82-  
15 3.76 (0.5 H, m), 3.68-3.62 (0.5 H, m), 3.28-3.21 (0.5H, m), 3.19-3.12 (0.5H, m), 3.07-2.98 (2H, m), 2.78-2.48 (4H, m).

The resulting product was converted to 106a by the method described to prepare compound H (StepD) to  
20 afford the title compound as a white solid (17%): <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.54-6.98 (9H, m), 5.58-5.44 (1H, m), 4.8-4.2 (4H, m), 3.96-3.3 (2H, m), 3.30-3.05 (1H, m), 2.98-2.25 (5H, m).

- [2-Oxo-5-(3-phenylpropionyl)-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid methyl  
25 ester (104b). Anhydrous hydrogen chloride was bubbled into a solution of (3(S)-tert-butoxycarbonylamino-2-oxo-2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-yl)acetic acid methyl ester (103, 1g, 2.86mmol) in 25

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ml of ethyl acetate for 2 minutes then stirred for 1 hour at room temperature. The reaction was evaporated to give 2-oxo-3(S)-amino-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl acetic acid methyl ester hydrochloride as a white solid.

The hydrochloride salt was suspended into 20 ml of dichloromethane and cooled to 0 °C. Triethylamine (1.6 ml, 11.5 mmol) was added to the suspension followed by the dropwise addition of dihydrocinnamoyl chloride (0.9 ml, 6 mmol). The mixture was warmed to room temperature and stirred for 18 hours. The mixture was diluted with 25 ml of dichloromethane and washed twice with 50 ml of water and once with 50 ml of brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated to give a viscous, yellow oil that was purified by flash chromatography eluting with 1:1 ethyl acetate/dichloromethane to afford 1.35 g (92%) of the title product as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.45-7.02 (14 H, m), 6.37-6.32 (1H, d), 4.78-4.72 (1H, m), 4.52-4.3 (3H, m), 3.82-3.77 (1H, m), 3.74 (3H, s), 3.03-2.87 (4H, m), 2.58-2.45 (2H, m), 2.45-2.35 (1H, m), 2.25-2.16 (1H, m).

[2-Oxo-5-(3-phenylpropionyl)-3-(3(S)-phenylpropionylamino)-2,3,4,5-

tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid (105b). [2-Oxo-5-(3-phenylpropionyl)-3-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid methyl ester (104b; 680 mg, 1.32 mmol) was hydrolyzed by the procedure used to hydrolyze 105a to afford 645 mg (98%) of the title compound as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.56 (1H, br. s), 7.5-7.42 (1H, m), 7.35-6.95 (14H,

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m), 4.95-4.88 (1H, m), 4.64-4.55 (1H, d), 4.54-4.45 (1H, t), 4.15-4.05 (1H, d), 3.75 (1H, m), 3.05-2.75 (4H, m), 2.58-2.45 (2H, m), 2.45-2.20 (1H, m), 2.25-2.14 (1H, m).

- 5 2-Oxo-3(S)-(2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-phenyl-propionyl-amino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetyl-amino)butyric acid (106b). [2-Oxo-5-(3-phenylpropionyl)-3-(3-phenylpropionylamino)-2,3,4,5-
- 10 tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid and 3-amino-4-oxobutyric acid tert-butylester semicarbazone were coupled by the procedure used in the preparation of compound K (step A) to give 350 mg (85%) of a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.05 (1H, br. s), 7.58-7.55
- 15 (1H,d), 7.5-7.35 (1H, m), 7.35-6.95 (14 H, m), 6.75-6.72 (1H, d), 6.25 (1H, br. s), 5.25 (1H, br. s), 4.95-4.88 (1H, m), 4.8-4.72 (1H, m), 4.55-4.4 (2H, m), 3.92-3.88 (1H, d), 3.73-3.68 (1H, m), 2.95-2.8 (4H, m), 2.8-2.72 (1H, m), 2.62-2.55 (1H, m), 2.55-2.45 (2H, m),
- 20 2.4-2.32 (1H, m), 2.2-2.12 (1H, m), 1.45 (9H, s). 4-Oxo-3-(2-[2-oxo-5-(3-phenylpropionyl)-3-(3-phenyl-propionyl -amino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-acetyl-amino)butyric acid tert-butyl ester semicarbazone was
- 25 deprotected as described in the preparation of compound K (step C) to give 118 mg (47%) of the title compound as a white solid. <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.48-6.95 (14 H, m), 4.65-4.15 (6H, m), 3.5-3.4 (1H, m), 2.85-2.72 (4H, m), 2.65-2.5 (1H, m), 2.5-2.34 (3H, m), 2.34-2.15 (2H, m).
- 30 [5-Benzyl-2-oxo-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-yl]acetic acid

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methyl ester (104c). [2-Oxo-3-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo-  
[b][1,4]diazepin-1-yl]acetic acid methyl ester (104a;  
500 mg, 1.31 mmol), calcium carbonate (155 mg, 1.58  
5 mmol), and benzyl bromide (170  $\mu$ l, 1.44 mmol) were  
taken into 10 ml of dimethylformamide and heated to 80  
°C for 8 hours. The mixture was diluted with 150 ml of  
ethyl acetate and washed 4 times with 50 ml of water.  
The organic layer was dried over anhydrous sodium  
10 sulfate, filtered, and evaporated to give a viscous,  
yellow oil that was purified by flash chromatography  
eluting with dichloromethane/ethyl acetate (8:2) to  
give 460 mg (75%) of the title compound as a white  
solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.34-7.05 (14 H, m), 6.32-6.28  
15 (1H, d), 4.84-4.76 (1H, d), 4.76-4.70 (1H, m), 4.43-  
4.37 (1H, d), 4.26-4.18 (1H, d), 4.06-4.00 (1H, d),  
3.79 (3H, s), 3.45-3.37 (1H, m), 3.02-2.95 (1H, m),  
2.90-2.82 (2H, m), 2.5-2.34 (2H, m).

[5-Benzyl-2-oxo-3(S)-(3-phenylpropionylamino)-2,3,4,5-  
20 tetrahydro-benzo[b][1,4]diazepin-1-yl]acetic acid  
(105c) was prepared by the hydrolysis of the ester  
(102c) by the procedure reported in Example 105a to  
give 450 mg (98%) of the title compound as a white  
solid:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.5-7.05 (14 H, m), 6.4 (1H,  
25 br. s), 4.85-4.55 (2H, m), 4.5-4.21 (2H, m), 4.12-3.92  
(1H, d), 3.45-3.3 (1H, m), 3.1-2.8 (3H, m), 2.55-2.28  
(3H, m).

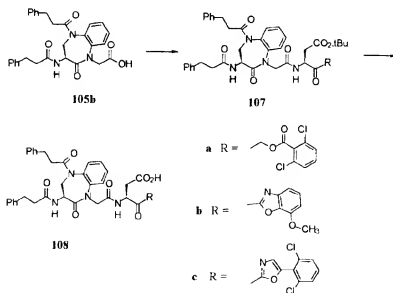
3(S)-(2-[5-Benzyl-2-oxo-3-(3(S)-phenylpropionylamino)-  
2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-  
30 acetylamino)-4-oxobutyric acid (106c). [5-Benzyl-2-



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oxo-3(S)-{3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b[1,4]diazepin-1-yl]acetic acid and 3(S)-amino-4-oxobutyric acid tert-butylester semicarbazone were coupled by the procedure used in the preparation of compound K (step A) and to afford 260 mg (85%) of a white solid:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.35-7.0 (15 H, m), 4.94-4.88 (1H, m), 4.68-4.58 (1H, d), 4.57-4.52 (1H, m), 4.41-4.34 (2H, d), 4.3-4.23 (1H, d), 4.1-4.04 (1H, d), 3.18-3.11 (1H, m), 3.09-2.98 (1H, m), 2.78-2.72 (2H, t), 2.65-2.57 (1H, m), 2.42-2.33 (3H, m).

3(S)-{2-[5-Benzyl-2-oxo-3(S)-{3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b[1,4]diazepin-1-yl]-acetylaminol-4-oxobutyric acid tert-butyl ester semicarbazone was deprotected as described in the preparation of compound K (step C) to give 168 mg (81%) of the title compound as a white solid.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.37-7.0 (14H, m), 4.75-4.62 (1H, m), 4.6-4.45 (2H, m), 4.4-4.21 (2H, m), 4.15-3.95 (2H, m), 3.15-3.0 (2H, m), 2.82-2.67 (2H, m), 2.65-2.52 (1H, m), 2.5-2.32 (3H, m).



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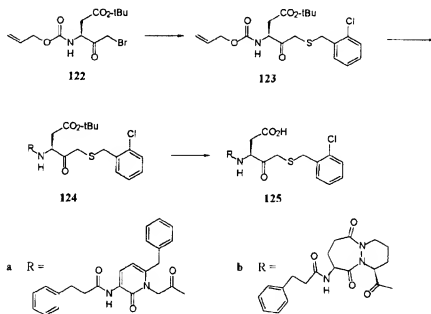
2,6-Dichlorobenzoic acid 4-tert-butoxycarbonyl-2-oxo-3(S)-(2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetyl-amino)butyl ester (107a). The resulting semicarbazone was prepared by the coupling of compound 105b and t-butyl 3-(allyloxycarbonylamino)-4-oxo-5-(2,6-dichlorobenzoyloxy)pentanoate (WO 93 16710) as described in compound 56a to give 256 mg (58%) of the title compound as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.45-7.04 (17H, m), 6.45-6.34 (2H, m), 5.28-5.21 (1H, m), 5.1-5.0 (1H, m), 4.95-4.90 (1H, m), 4.75-4.70 (1H, m), 4.55-4.44 (1H, m), 4.32-4.22 (1H, dd), 3.99-3.85 (1H, dd), 3.85-3.76 (1H, m), 3.06-2.83 (5H, m), 2.83-2.74 (1H, m), 2.6-2.44 (2H, m), 2.43-2.33 (1H, m), 2.24-2.15 (1H, m), 1.45 (9H, s).

2,6-Dichlorobenzoic acid 4-carboxy-2-oxo-3(S)-(2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetyl-amino)butyl ester (108a) was prepared from 107a by the method described for compound 57a which afforded 156 mg (68%) of the title compound as a white solid. <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.5-6.9 (17H, m), 5.16-5.02 (1H, dd), 4.88-4.71 (2H, m), 4.62-4.44 (2H, m), 4.42-4.28 (2H, m), 4.27-4.18 (1H, m), 3.47-3.41 (1H, m), 2.90-2.60 (5H, m), 2.46-2.4 (2H, m), 2.39-2.18 (2H, m).

4-(7-Methoxybenzoxazol-2-yl)-4-oxo-3(S)-(2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-acetyl-amino)butyric acid (108b) was prepared by the method

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described for compound **69a** to give the title compound (50%) as a white solid.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.41-6.88 (17H, m), 5.6-5.55 (0.5H, t), 5.48-5.43 (0.5H, t), 4.64-4.45 (2H, m), 4.45-4.30 (1H, m), 3.93 (1.5H, s), 3.90 (1.5H, s), 3.47-3.34 (1H, m), 3.10-2.85 (2H, m), 2.84-2.63 (5H, m), 2.6-2.4 (2H, m), 2.3-2.1 (2H, m).



**t-Butyl (3S) N-(allyloxycarbonyl)-3-amino-5-(2-chlorophenylmethylthio)-4-oxo-pentanoate (123).**

Potassium fluoride (273mg, 4.70mmol) and then 2-chlorophenylmethyl thiol (373mg, 2.35mmol) were added to a stirred solution of (3S) t-butyl N-(allyloxycarbonyl)-3-amino-5-bromo-4-oxo-pentanoate (122; 749mg, 2.14mmol; WO 93 16/10) in dimethylformamide (20ml). The mixture was stirred for 3.5h, quenched with water (50ml) and extracted with ethyl acetate (2 x 50ml). The combined organic extracts were washed with water (4 x 50ml) then brine

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(50ml). They were dried ( $\text{MgSO}_4$ ) and concentrated to afford an oil which was purified by flash chromatography (10-35% ethyl acetate/hexane) to afford 832 mg (91%) of a colourless solid: mp. 45-6 °C;  $[\alpha]_D^{20}$  -19.0° (c 1.0,  $\text{CH}_2\text{Cl}_2$ ); IR (film) 3340, 2980, 2935, 1725, 1712, 1511, 1503, 1474, 1446, 1421, 1393, 1368, 1281, 1244, 1157, 1052, 1040, 995, 764, 739;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.36 (2H, m), 7.21 (2H, m), 5.91 (2H, m), 5.27 (2H, m), 4.76 (1H, m), 4.59 (2H, d), 3.78 (2H, s), 3.36 (2H, m), 2.91 (1H, dd), 2.74 (1H, dd), 1.43 (9H, s). Anal. Calcd for  $\text{C}_{20}\text{H}_{26}\text{ClNO}_5\text{S}$ : C, 56.13; H, 6.12; N, 3.27; S, 7.49. Found: C, 56.08; H, 6.11; N, 3.26; S, 7.54. MS (C.I.) 430/28 ( $\text{M}^+ + 1$ , 3%), 374/2 (100).

**t-Butyl (3S) 3(2(6-benzyl-1,2-dihydro-2-oxo-3(3-phenylpropionylamino)-1-pyridyl)acetyl-amino-5-(2-chlorophenylmethylthio)-4-oxopentanoate (124a).** 6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionylamino)-pyridyl acetic acid (**52b**; 300mg, 0.76mmol) in THF (7ml) was stirred with 1-hydroxybenzotriazole (205mg, 1.52mmol) and 1-(3-dimethylaminopropyl-ethylcarbodiimide hydrochloride). After 3 min, water (12 drops) was added and the mixture stirred 10min then treated with t-butyl (3S) N-(allyloxycarbonyl)-3-amino-5-(2-chlorophenylmethylthio)-4-oxopentanoate (**123**) (325mg, 0.76mmol), bis (triphenylphosphine) palladium II chloride (20mg) and tributyltin hydride (0.6ml, 2.28mmol). The mixture was stirred for 5h at room temperature, poured into ethyl acetate and washed with aqueous 1M HCl (x2), aqueous sodium bicarbonate, brine, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was triturated with pentane and the supernatant discarded. Chromatography (silica gel, 50% ethyl acetate/hexane)

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afforded a colourless foam (439mg, 81%):  $[\alpha]_D^{22} -18.3^\circ$   
(c 0.5,  $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3356, 3311, 1722, 1689, 1646,  
1599, 1567, 1513, 1367, 1154;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.39 (1H,  
d), 8.23 (1H, s), 7.24 (14H, m), 6.16 (1H, d), 4.95  
5 (1H, m), 4.63 (2H, m), 4.02 (2H, s), 3.74 (2H, s),  
3.27 (2H, s), 2.85 (6H, m), 1.40 (9H, s). Anal. Calcd  
for  $\text{C}_{39}\text{H}_{42}\text{ClN}_3\text{O}_6\text{S}$ : C, 65.39; H, 5.91; N, 5.87. Found:  
C, 65.51; H, 5.99; N, 5.77.

t-Butyl[3*S*(1*S*,9*S*)]-3-(6,10-dioxo-1,2,3,4,7,8,9,10-  
10 octahydro)-9-(3-phenylpropionylamino)-6H-  
pyridazine[1,2-a][1,2]diazepine-1-carboxamido-5-(2-  
chlorophenylmethylthio)-4-oxopentanoate (124b) was  
prepared by a similar method as 124a from the thioether  
123 and 3*S*(1*S*,9*S*)-3-(6,10-dioxo-1,2,3,4,7,8,9,10-  
15 octahydro)-9-(3-phenylpropionylamino)-6H-  
pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid (45a)  
to afford 452mg (50%) of colourless foam: mp 55-7  $^\circ\text{C}$ ;  
 $[\alpha]_D^{22} -94.0^\circ$  (c 0.12,  $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3288, 2934,  
1741, 1722, 1686, 1666, 1644, 1523, 1433, 1260, 1225,  
20 1146, 757;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.35 (3H, m), 7.20 (7H, m),  
6.46 (1H, d), 5.21 (1H, m), 4.97 (2H, m), 4.56 (1H, m),  
3.75 (2H, s), 3.25 (3H, m), 2.93 (5H, m), 2.71 (1H,  
dd), 2.55 (2H, m), 2.30 (1H, m), 1.92 (3H, m), 1.66  
(2H, m), 1.42 (9H, s). Anal. Calcd for  $\text{C}_{35}\text{H}_{43}\text{ClN}_4\text{O}_7\text{S}$ .  
25 0.25 $\text{H}_2\text{O}$ : C, 59.73; H, 6.23; Cl, 5.04; N, 7.96; S,  
4.56. Found: C, 59.73; H, 6.19; Cl, 5.10; N, 7.79; S,  
4.58. MS (-FAB) 697 (M-1, 100).

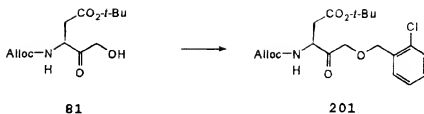
(3*S*) 3(2(6-Benzyl-1,2-dihydro-2-oxo-3-(3-  
phenylpropionylamino)-1-pyridyl)acetyl-amino-5-(2-  
30 chlorophenylmethylthio)-4-oxopentanoic acid (125a).

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t-Butyl-3(2(6-benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionylamino)-1-pyridyl)acetyl-amino-5-(2-chlorophenylmethylthio)-4-oxopentanoate (**124a**) (400mg, 0.56mmol) in dichloromethane (3ml) at 0 °C was treated  
5 with trifluoroacetic acid (3ml) and stirred at 0 °C for 1h and room temperature for 0.5h. The solution was concentrated then redissolved in dichloromethane and reconcentrated. This procedure was repeated three times. The residue was stirred in ether for 1hr and  
10 filtered to yield a colourless solid (364mg, 99%): mp. 165-7 °C;  $[\alpha]_D^{22}$  -27.7 ° (c 0.2, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3289, 1712, 1682, 1657, 1645, 1593, 1562, 1527, 1497, 1416, 1203, 1182; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.47 (1H, d), 8.21 (1H, s), 7.70 (1H, d), 7.22 (14H, m), 6.24 (1H, d), 5.03  
15 (1H, m), 4.65 (2H, m), 4.06 (2H, s), 3.69 (2H, m), 3.23 (2H, m), 2.88 (6H, m).

[3S(1S,9S)]-3-(6,10-dioxo-1,2,3,4,7,8,9,10-octahydro)-9-(3-phenylpropionyl-amino)-6H-pyridazine[1,2-a][1,2]diazepine-1-carboxamido-5-(2-chlorophenyl-methylthio)-4-oxopentanoic acid (**125b**),  
20 was prepared by a similar method as **125a** from the t-butyl ester **124b** to afford 362mg (93%) of colourless powder: mp 76-80 °C;  $[\alpha]_D^{21}$  -134 ° (c 0.10, MeOH); IR (KBr) 3309, 2935, 1725, 1658, 1528, 1445, 1417, 1277,  
25 1019, 1175; <sup>1</sup>H NMR (D<sub>6</sub>-DMSO) δ 8.80 (1H, d), 8.19 (1H, d), 7.31 (9H, m), 5.09 (1H, m), 4.74 (1H, m), 4.63 (1H, m), 4.35 (1H, m), 3.76 (2H, m), 3.28 (3H, m), 2.80 (5H, m), 2.52 (4H, m), 2.16 (2H, m), 1.90 (3H, m). Anal. Calcd for C<sub>31</sub>H<sub>35</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>7</sub>S. 0.25H<sub>2</sub>O: C, 57.49; H, 5.53; N, 8.65; S, 4.95. Found: C, 57.35; H, 5.43; N, 8.45; S, 4.88. MS (-FAB) 641 (M-1, 100).

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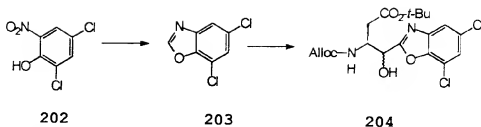
2-Chlorophenylmethyliodide. A mixture of 2-chlorophenylmethylbromide (4g, 19.47mmol) and NaI (14g, 97.33mmol) in acetone (40ml) was stirred under reflux for 1 hour. The reaction mixture was cooled, filtered and concentrated *in vacuo*. The residue was triturated with hexane and filtered. The solution was concentrated *in vacuo*, and the resulting oil purified by flash chromatography (silica, hexane) to afford the title compound (4.67g, 63%) as an oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )

10  $\delta$  7.34 (4H, m), 4.54 (2H, s).

(3S) t-Butyl N-(allyloxycarbonyl)-3-amino-5-(2-chlorophenylmethoxy)-4-oxopentanoate (201). (3S) t-Butyl N-(allyloxycarbonyl)-3-amino-5-hydroxy-4-oxopentanoate (**81**, Chapman, et al., Bioorg. & Med. Chem. Lett., 2, pp. 613-618 (1992) 0.144g, 0.5mmol) and 2-chlorophenylmethyliodide (0.569g, 1.5mmol) in  $\text{CH}_2\text{Cl}_2$  (4ml) were stirred vigorously with silver oxide (0.231g, 1mmol) and heated at 38 °C for 40 hours. The reaction mixture was cooled, filtered and the filtrate evaporated. The residue was purified by flash chromatography (silica, 0-20% ethylacetate in hexane) to afford the product as a colourless oil (0.138g, 67%):  $[\alpha]_D^{24} +3.9^\circ$  (c 1.3,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.37 (4H, m), 5.88 (2H, m), 5.26 (2H, m), 4.69 (2H, s), 4.57 (3H, m), 4.50 (1H, d), 4.35 (1H, d), 3.03 (1H, dd), 2.76 (1H, dd), 1.42 (9H, s).

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- 5,7-Dichlorobenzoxazole (**203**). A solution of 2,4-dichloro-6-nitrophenol (**202**, 40g containing 20% moisture) in EtOAc (500ml) was dried using  $\text{MgSO}_4$ , filtered and the filter cake washed with a little EtOAc. Platinum on carbon (5% sulphided - 2g) was added and the mixture hydrogenated until uptake of  $\text{H}_2$  ceased. Triethyl orthoformate (160ml) and p-toluene sulphonic acid (160mg) were added and the mixture refluxed for 4h. After cooling and removal of spent catalyst by filtration the solution was washed with sat.  $\text{NaHCO}_3$  solution, water and brine, dried with  $\text{MgSO}_4$  and evaporated to dryness. Trituration with hexane gave a solid which was collected by filtration, washed with hexane and dried to give the title compound (25.5g, 88%) as a crystalline solid: mp 98-99 °C; IR (KBr) 3119, 1610, 1590, 1510, 1452, 1393, 1296, 1067, 850;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.16 (1H, s), 7.69 (1H, d,  $J = 1.9$ ), 7.42 (1H, d,  $J = 1.9$ ); Anal. Calcd for  $\text{C}_7\text{H}_3\text{Cl}_2\text{NO}$ : C, 44.72; H, 1.61; N, 7.45; Cl, 37.70. Found: C, 44.84; H, 1.69; N, 7.31; Cl, 37.71.

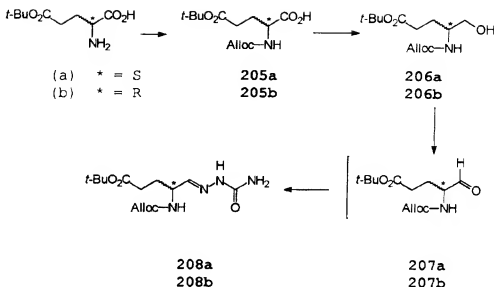
- (3S,4RS) t-Butyl N-(allyloxycarbonyl)-3-amino-4-hydroxy-4-(5,7-dichlorobenzoxazol-2-yl)butanoate (**204**). Magnesium bromide was prepared by reaction of Mg (7.45g, 0.30mole) in THF (516ml) with  $\text{I}_2$  (50mg) and 1,2-dibromoethane (26.3ml, 57.3g, 0.30mole) at reflux for 2h and then cooling to -40 °C. To the above was



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added rapidly via cannula a solution of 2-lithio-5,7-dichlorobenzoxazole at 70 °C (prepared from 5,7-dichlorobenzoxazole (**203**, 28.9g, 0.154mole) and butyl lithium (100ml 1.52M in hexane) in THF (150ml) at -70 °C). The mixture was stirred at -40 °C for 1h and then cooled to -70 °C before adding a solution of (3S) t-butyl N-(allyloxycarbonyl)-3-amino-4-oxo-butanoate (Chapman, et al., Bioorg. & Med. Chem. Lett., 2, pp. 613-618 (1992)) (20.3g, 0.078mole) in THF (160ml) at less than -60 °C. The reaction was allowed to warm to ambient temperature and was stirred for 16h before quenching with ammonium chloride solution and extracting with 1:1 hexane:ethylacetate 600ml. The organic solution was washed with water and brine, dried with MgSO<sub>4</sub> and evaporated to a syrup (52.9g). Flash chromatography (SiO<sub>2</sub> 250g -11 aliquots of 1:1 hexane: CH<sub>2</sub>Cl<sub>2</sub> x2, CH<sub>2</sub>Cl<sub>2</sub>, 5% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>, 10% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>, 20% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>) gave impure product 24.6g which on further chromatography (SiO<sub>2</sub> 1:1 hexane:ether) give the title compound as a golden-brown glass (22.7g, 64%); IR (film) 3343, 2980, 1723, 1712, 1520, 1456, 1398, 1369, 1254, 1158, 993; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.60 (1H, m), 7.37 (1H, m), 5.72 (1H, m), 5.64 (0.5H, d), 5.10 (2.5H, m), 4.7-4.3 (4H, m), 2.9-2.6 (2H, m), 1.46 and 1.42 (9H combined, 2 x s). MS ES<sup>+</sup> Da/e 445 (M + 1)<sup>+</sup> C1 35 62%, 447 (M + 1)<sup>+</sup> C1 37 40%, 389 100%.

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**(2S)-N-Allyloxycarbonyl-5-(1,1-dimethylethyl) glutamate**

(205a). To a mixture of THF (200ml) and water (100ml) containing NaHCO<sub>3</sub> (16.6g, 0.2mol) was added glutaric acid t-butyl ester (10g, 49.2mmol) and then dropwise over 20 minutes allyl chloroformate (6.8ml, 64mmol). The mixture was stirred for 2 hours, extracted with EtOAc, washed with a sat. hydrogenocarbonate solution, water and a sat. salt solution, dried and evaporated to an oil **205a** (9.5g, 67.2%); [ $\alpha$ ]<sub>D</sub><sup>20</sup> -6 ° (c 1.5, MeOH)

<sup>1</sup>H NMR (D<sub>6</sub>-DMSO)  $\delta$  6.10 (1H, d), 5.96-5.88 (1H, m), 5.31-5.12 (2H, m), 4.45 (2H, m), 3.90-3.84 (1H, m), 2.18 (2H, m), 1.85-1.76 (2H, m), 1.36 (9H, s).

**(2R)-N-Allyloxycarbonyl-5-(1,1-dimethylethyl) glutamate**

(205b), was prepared by an analogous method to **205a** to afford a colourless oil (6.27g, 88%); [ $\alpha$ ]<sub>D</sub><sup>20</sup> +16 ° (c 0.095, MeOH); IR (KBr) 3678, 3332, 3088, 2980, 2937, 1724, 1530, 1453, 1393, 1370, 1331, 1255, 1155, 1056, 995, 935, 845, 778, 757, 636, 583; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$

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9.24 (1H, broad s), 5.94-5.79 (1H, m), 5.58 (1H, d), 5.33-5.17 (2H, m), 4.55 (2H, d), 4.38-4.31 (1H, m), 2.41-1.95 (4H, m), 1.42 (9H, s); Anal. Calcd for  $C_{13}H_{21}NO_6$ : C, 54.35; H, 7.37; N, 4.88. Found: C, 54.4; H, 7.5; N, 4.8.

(4S) t-Butyl N-allyloxycarbonyl-4-amino-5-hydroxypentanoate (206a). To a solution of 205a (3.6g, 12.5mmol) in THF (100ml) at 0 °C was added N-methylmorpholine (1.5ml, 13mmol) followed by isobutyl chloroformate, (1.1ml, 13mmol). After 15 minutes, this mixture was added to a suspension of  $NaBH_4$  (0.95g, 25mmol) in THF (100ml) and MeOH (25ml) at -78 °C. After 2 hours at -70 °C, the mixture was quenched with acetic acid, diluted with EtOAc, washed with a sat. hydrogenocarbonate solution 3 times, water and a sat. solution of salt, dried and evaporated. Flash chromatography (2% MeOH in  $CH_2Cl_2$ ) afforded 206a as a colourless oil (2.4g, 70%):  $[\alpha]_D^{20}$  -10 ° (c 3.88,  $CH_2Cl_2$ );  $^1H$  NMR ( $CDCl_3$ )  $\delta$  5.84 (1H, m), 5.34-5.17 (3H, m), 4.56-4.53 (2H, m), 3.68-3.59 (2H, m), 2.98 (1H, m), 2.40-2.30 (2H, t), 1.84-1.78 (2H, m), 1.43 (9H, s); Anal. Calcd for  $C_{13}H_{23}NO_5$ : C, 57.13; H, 8.48; N, 5.12. Found: C, 57.1; H, 8.6; N, 6.0

(4R) t-Butyl N-allyloxycarbonyl-4-amino-5-hydroxypentanoate (206b), was prepared by an analogous method to 206a which afforded the title compound as a light yellow oil (3.42g, 57%):  $[\alpha]_D^{20}$  +14 (c 0.166, MeOH); IR (KBr) 3341, 3083, 2976, 2936, 2860, 1724, 1533, 1454, 1419, 1369, 1332, 1251, 1156, 1062, 997, 933, 846, 777, 647;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  5.98-5.81 (1H, m), 5.35-5.10 (3H, m), 4.55 (2H, d), 3.70-3.56 (3H, m),

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2.50-2.47 (1H, broad s), 2.37-2.30 (2H, m), 1.89-1.74 (2H, m), 1.44 (9H, s); Anal. Calcd for  $C_{13}H_{23}NO_5$ : C, 57.13; H, 8.48; N, 5.12. Found: C, 56.9; H, 8.6; N, 5.6

- 5 **(4S) t-Butyl N-Allyloxycarbonyl-4-amino-5-oxopentanoate (207a)**. To a solution of DMSO (1.51g, 19.3mmol) in  $CH_2Cl_2$  (25ml) at -70 °C was added oxalyl chloride (1.34g, 19.3mmol). After 10 minutes at -70 °C, a solution of (206a) (2.4g, 8.8mmol) in  $CH_2Cl_2$  (10ml) was  
10 added dropwise and the mixture stirred for 15 minutes at -70 °C. Diisopropylethylamine (3.4g, 26.3mmol) was added and the mixture stirred at -25 °C for 15 minutes then diluting with EtOAc (50ml) washed with a solution of sodium hydrogen sulfate 2M, concentrated to give an  
15 oil which was used immediately without purification:  $^1H$  NMR ( $CDCl_3$ )  $\delta$  9.5 (1H, s), 6.0-5.5 (2H, m), 5.5-5.1 (2H, m), 4.5 (2H, m), 4.2 (1H, m), 2.4-2.10 (2H, m), 2.05 (2H, m), 1.36 (9H, s).

- (4R) t-Butyl N-Allyloxycarbonyl-4-amino-5-oxopentanoate (207b)**, was prepared by an analogous method to 207a  
20 which afforded an oil (2.95g, 96%) which was used without further purification in the next step:  $[\alpha]_D^{20}$  +21 ° (c 0.942, MeOH);  $^1H$  NMR ( $CDCl_3$ )  $\delta$  9.58 (1H, s), 6.05-5.80 (1H, m), 5.57 (1H, broad s), 5.35-5.18 (2H, m), 4.56 (2H, d), 4.34-4.24 (1H, m), 2.38-2.16 (3H, m),  
25 1.96-1.73 (1H, m), 1.43 (9H, s).

- (4S) t-Butyl N-Allyloxycarbonyl-4-amino-5-oxopentanoate semicarbazone (208a)**. To a solution of 207a (2.39g, 8.8mmol), in MeOH (20ml) was added sodium acetate  
30 (0.72g, 8.8mmol) and semicarbazide (0.98g, 8.8mmol)

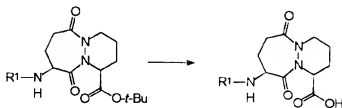
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stirred overnight, concentrated and diluted with  $\text{CH}_2\text{Cl}_2$  (100ml), washed with water, dried and concentrated.

Flash chromatography (2% MeOH in  $\text{CH}_2\text{Cl}_2$ ) afforded **208a** (2.10g, 73%) as an oil:  $[\alpha]_D^{20}$  -21 (c 2.55,  $\text{CH}_2\text{Cl}_2$ );

<sup>1</sup>H NMR ( $\text{CDCl}_3$ )  $\delta$  9.98 (1H, s), 7.27 (1H, d), 5.8 (1H, m), 5.5 (1H, d), 5.35-5.19 (2H, m), 4.58 (2H, m), 4.14 (1H, m), 2.37 (2H, t), 2.09 (1H, m), 2.0-1.75 (2H, m);  
Anal. Calcd for  $\text{C}_{14}\text{H}_{24}\text{N}_4\text{O}_5$ : C, 51.21; H, 7.37; N, 17.06. Found: C, 50.2; H, 7.3; N, 16.1

10 **(4R) t-Butyl N-Allyloxycarbonyl-4-amino-5-oxopentanoate semicarbazone (208b)**, was prepared by an analogous method to **208a** which afforded a glassy oil (2.37g, 66%):  $[\alpha]_D^{20}$  +30 (c 0.26,  $\text{CHCl}_3$ ); IR (KBr) 3476, 3360, 2979, 2923, 1700, 1586, 1527, 1427, 1394, 1369, 1338,  
15 1253, 1156, 1060, 997, 929, 846, 775; <sup>1</sup>H NMR ( $\text{CDCl}_3$ )  $\delta$  9.87 (1H, s), 7.09 (1H, d), 6.05-5.75 (3H, m), 5.58 (1H, d), 5.32-5.16 (2H, m), 4.54 (2H, d), 4.35 (1H, m), 2.32-2.26 (2H, m), 2.15-1.55 (2H, m), 1.41 (9H, s);  
Anal. Calcd for  $\text{C}_{14}\text{H}_{24}\text{N}_4\text{O}_5$ : C, 51.21; H, 7.37; N, 17.06. Found: C, 51.0; H, 7.5; N, 16.7.



211 (b)  $\text{R}^1 = \text{MeSO}_2$   
(c)  $\text{R}^1 = \text{MeCO}$   
(d)  $\text{R}^1 = \text{PhCH}_2\text{OCO}$   
(e)  $\text{R}^1 = \text{PhCO}$   
25 (f)  $\text{R}^1 = \text{Fmoc}$

212 (b)  $\text{R}^1 = \text{MeSO}_2$   
(c)  $\text{R}^1 = \text{MeCO}$   
(d)  $\text{R}^1 = \text{PhCH}_2\text{OCO}$   
(e)  $\text{R}^1 = \text{PhCO}$   
(f)  $\text{R}^1 = \text{Fmoc}$

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- (1*S*,9*S*) t-Butyl 6,10-dioxo-9-methylsulfonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxylate (211b). A solution of t-butyl 9-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (GB 2,128,984; 831mg, 2.79mmol) and diisopropylethylamine (1.22ml, 6.99mmol, 2.5 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (10ml) under dry nitrogen was treated with methanesulphonyl chloride (237μl, 3.07mmol 1.1 equiv).
- The mixture was stirred for 1h, diluted with EtOAc (75ml) and washed with saturated NaHCO<sub>3</sub> (50ml) and saturated aqueous sodium chloride (30ml), dried (MgSO<sub>4</sub>) and concentrated. Flash chromatography (10-35% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>) afforded 211b (806mg, 77%) as a colourless solid: mp 68-70 °C; [α]<sub>D</sub><sup>23</sup> -109 (c 1.09, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3270, 2980, 2939, 1735, 1677, 1458, 1447, 1418, 1396, 1370, 1328, 1272, 1252, 1232, 1222, 1156, 1131, 991; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 6.15 (1H, d), 5.31 (1H, m), 4.65-4.11 (2H, m), 3.47 (1H, m) 2.99 (3H, s), 2.89 (1H, m), 2.72-2.51 (2H, m), 2.34 (1H, m), 2.26 (1H, m), 2.05-1.62 (4H, m), 1.47 (9H, s); Anal. Calcd for C<sub>15</sub>H<sub>23</sub>N<sub>3</sub>O<sub>6</sub>S: C, 47.97; H, 6.71; N, 11.19; S, 8.54. Found: C, 48.28; H, 6.68; N, 10.86; S, 8.28. MS (+FAB) 376 (M<sup>+</sup> + 1, 66%), 320 (100).
- (1*S*,9*S*) t-Butyl 9-acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino [1,2-a]-[1,2]diazepine-1-carboxylate (211c). Acetic anhydride (307mg, 3.01mmol) was added to a stirred mixture of t-butyl 9-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (GB 2,128,984; 813.7mg, 2.74mmol), diisopropylethylamine (884mg, 6.84mmol) and CH<sub>2</sub>Cl<sub>2</sub>

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(20ml). The mixture was kept for 1h then diluted with EtOAc, washed with NaHCO<sub>3</sub> solution then brine, dried (MgSO<sub>4</sub>) and concentrated to yield a colourless oil. The product was purified by flash chromatography (0.5-  
5 8% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to afford **211c** (804mg, 71%) of colourless powder: mp 162-3 °C;  $[\alpha]_D^{23}$  -109 (c 1.03, CH<sub>2</sub>Cl<sub>2</sub>); IR(KBr) 3358, 2974, 1733, 1693, 1668, 1528, 1462, 1431, 1406, 1371, 1278, 1271, 1250, 1233, 1217, 1154, 1124;  $\delta$  <sup>1</sup>H NMR (CDCl<sub>3</sub>) d 6.32 (1H, d), 5.29-5.25  
10 (1H, m), 4.98-4.85 (1H, m), 4.68-4.58 (1H, m), 3.55-3.39 (1H, m), 2.91-2.66 (2H, m), 2.39-2.18 (2H, m), 2.03 (3H, s), 1.88-1.64 (4H, m), 1.47 (9H, s); Anal. Calcd for C<sub>16</sub>H<sub>25</sub>N<sub>3</sub>O<sub>5</sub>: C, 56.62; H, 7.43; N, 12.38. Found: C, 56.62; H, 7.43; N, 12.36; MS (+ FAB) 340 (M<sup>+</sup>  
15 + 1, 40%), 284 (100).

(1*S*,9*S*) t-Butyl 9-(benzyloxycarbonylamino)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (**211d**). Benzyl chloroformate (1.07g) was added dropwise to a stirred ice cold  
20 mixture of the (1*S*,9*S*) t-butyl 9-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (GB 2,128,984; 1.55g, 5.21mmol), NaHCO<sub>3</sub> (0.66g, 7.82mmol), dioxan (32ml) and water (8ml). The mixture was kept at 5 °C for 15min  
25 then for 2h at room temperature. The mixture was diluted with EtOAc (50ml), washed twice with sat. NaHCO<sub>3</sub> solution, dried (MgSO<sub>4</sub>) and concentrated. The oily residue was purified by flash chromatography to afford **211d** (1.98g, 88%) of a colourless oil:  $[\alpha]_D^{24}$  -  
30 56.4 (c 1.0, CH<sub>2</sub>Cl<sub>2</sub>); IR(thin film) 3325, 2979, 2946, 1728, 1677, 1528, 1456, 1422, 1370, 1340, 1272, 1245, 1156, 1122, 1056, 916, 734, 699; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.29

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(5H, m), 5.81-5.72 (1H, m), 5.26-5.20 (1H, m), 5.05 (2H, s), 4.69-4.51 (2H, m), 3.48-3.36 (1H, m), 2.81-2.51 (2H, m), 2.34-2.19 (2H, m), 1.90-1.54 (4H, m), 1.41 (9H, s); Anal. Calcd for  $C_{22}H_{29}N_3O_6 \cdot H_2O$ : C, 58.79; H, 6.92; N, 9.35. Found: C, 59.10; H, 6.57; N, 9.25; MS (ES +) 454 ( $M^+Na$ , 87%), 432 ( $M^++1$ , 100).

(1S,9S) t-Butyl 9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxylate (211e). A solution of benzoyl chloride (1.61g, 11.47mmol) in  $CH_2Cl_2$  (15ml) was added dropwise to a stirred ice cold mixture of (1S,9S) t-butyl 9-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (GB 2,128,984; 3.1g, 10.43mmol), dry  $CH_2Cl_2$  (20ml) and diisopropylethylamine (4.54ml, 26.06mmol). The mixture was kept cold for 1h then left at room temperature for 0.5h. The mixture was diluted with  $CH_2Cl_2$ , washed twice with brine, dried ( $MgSO_4$ ) and concentrated. The residue was purified by flash chromatography (0-5% metha: 1 in  $CH_2Cl_2$ ) to afford 211e (4.0g, 96%) of a colourless glass: mp 74-76 °C;  $[\alpha]_D^{30}$  -75.0 ° (c 0.12,  $CH_2Cl_2$ ). IR (KBr) 3350, 2979, 2938, 1736, 1677, 1662, 1536, 1422, 1276, 1250, 1155;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  8.72 (2H, m), 7.53-7.40 (3H, m), 7.07 (1H, d,  $J$  = 7.2), 5.30 (1H, dd,  $J$  = 3.0, 5.8), 5.12 (1H, m), 4.66 (1H, m), 3.51 (1H, m), 2.90 (2H, m), 2.38 (1H, dd,  $J$  13.2, 6.8), 2.25 (1H, m), 1.9 (2H, m), 1.70 (1H, m). Anal. Calcd for  $C_{21}H_{27}N_3O_5 \cdot 0.5H_2O$ : C, 61.45; H, 6.88; N, 10.24. Found C, 61.69; H, 6.71; N, 10.18.

(1S,9S) t-Butyl 6,10-dioxo-9-(fluoren-9-ylmethoxy-carbonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-



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pyridazino[1,2-a][1,2]-diazepine-1-carboxylate (211f), was prepared in a similar manner to 211e, except 9-fluorenylmethylchloroformate was used instead of benzoylchloride to give a white glassy solid 211f.

- 5 (2.14g, 89%): mp 190-192 °C;  $[\alpha]_D^{25}$  -81.5 ° (c 0.1, CH<sub>2</sub>Cl<sub>2</sub>). IR (KBr) 3335, 2977, 1731, 1678, 1450, 1421, 1246, 1156, 742; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.60 (2H, m), 7.57 (2H, m), 7.50-7.26 (4H, m), 5.60 (1H, d, J = 7.8), 5.28 (1H, m), 4.67 (2H, m), 4.38 (2H, m), 4.23 (1H, m),  
10 3.59-3.41 (1H, m), 2.92-2.65 (2H, m), 2.41-2.21 (2H, m), 1.95-1.58 (4H, m), 1.47 (9H, s). MS(ES<sup>-</sup>, m/z): 520 (M<sup>+</sup> + 1, 97%), 179 (100%).

- (1S,9S) 6,10-Dioxo-9-methylsulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-  
15 [1,2-a][1,2]diazepine-1-carboxylic acid (212b), was synthesized by the same method as compound 212e (635mg, 85%) as a colourless powder: mp 209-12 °C;  $[\alpha]_D^{24}$  -132 (c 0.12, MeOH); IR (KBr) 3308, 2940, 1717, 1707, 1699, 1619, 1469, 1456, 1442, 1417, 1391, 1348, 1339, 1330,  
20 1310, 1271, 1247, 1222, 1175, 1152, 1133, 993, 976; <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 5.35 (1H, m), 4.58-4.48 (1H, m), 4.46-4.36 (1H, m), 3.60-3.42 (1H, m), 3.01-2.87 (1H, m), 2.95 (3H, s), 2.55-2.39 (1H, m), 2.32-2.20 (2H, m), 2.09-1.89 (2H, m), 1.78-1.62 (2H, m); Anal. Calcd for  
25 C<sub>11</sub>H<sub>11</sub>N<sub>3</sub>O<sub>6</sub>S: C, 41.37; H, 5.37; N, 13.16; S, 10.04. Found: C, 41.59; H, 5.32; N, 12.75; S, 9.76; MS(ES<sup>-</sup>). Accurate Mass calculated for C<sub>11</sub>H<sub>11</sub>N<sub>3</sub>O<sub>6</sub>S (MH<sup>+</sup>): 320.0916. Found: 320.0943.

- (1S,9S) 9-Acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-  
30 octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid (212c), was prepared from 211e the same

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method as compound **212e** as a white glassy solid (595mg, 77%): mp >250 °C;  $[\alpha]_D^{24}$  -153 (c 0.10, MeOH); IR (KBr) 3280, 2942, 1742, 1697, 1675, 1650, 1616, 1548, 1470, 1443, 1281, 1249, 1202, 1187, 1171;  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  5.35-5.31 (1H, m), 4.81-4.71 (1H, m), 4.61-4.46 (1H, m), 3.59-3.44 (2H, m), 3.11-2.94 (1H, m), 2.58-2.39 (1H, m), 2.36-2.19 (2H, m), 2.11-1.83 (3H, m), 1.99 (3H, s), 1.78-1.56 (2H, m); Anal. Calcd for  $\text{C}_{12}\text{H}_{17}\text{N}_3\text{O}_5$ : C, 50.88; H, 6.05; N, 14.83. Found: C, 50.82; H, 6.02; N, 14.58; MS (ES<sup>-</sup>) 282 (M-1, 100%): Accurate Mass calculated for  $\text{C}_{12}\text{H}_{18}\text{N}_3\text{O}_5$  ( $\text{MH}^+$ ): 284.1246. Found: 284.1258.

(1S,9S) 9-Benzoyloxycarbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-  
15 [1,2-a][1,2]diazepine-1-carboxylic acid (**212d**), was prepared from **211d** by the same method as compound **212e** as colourless crystals (170mg, 97%): mp 60-100 °C;  $[\alpha]_D^{22}$  -103 (c 0.10, MeOH); IR (KBr) 3341, 2947, 1728, 1675, 1531, 1456, 1422, 1339, 1272, 1248, 1221, 1174,  
20 1122, 1056, 982, 699;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.35 (5H, s), 5.65 (1H, d), 5.48-5.40 (1H, m), 5.10 (2H, s), 4.76-4.57 (2H, m), 3.49-3.30 (2H, m), 2.92-2.59 (2H, m), 2.40-2.27 (2H, m), 1.97-1.67 (4H, m); MS (ES<sup>-</sup>) 374 (M - 1, 100%). Accurate mass calculated for  $\text{C}_{16}\text{H}_{22}\text{N}_3\text{C}_6$  ( $\text{MH}^+$ ): 376.1509. Found: 376.1483. Accurate mass  
25 calculated for  $\text{C}_{16}\text{H}_{21}\text{N}_3\text{O}_6\text{Na}$  ( $\text{MNa}^+$ ): 398.1328. Found: 398.1315.

(1S,9S) 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-  
30 carboxylic acid (**212e**). TFA (20ml) was added to an ice cold stirred solution of the t-butyl ester **211e** (4.15g,

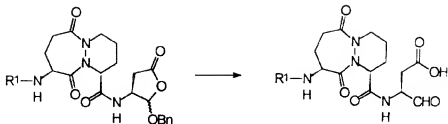
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10.34mmol) in dry  $\text{CH}_2\text{Cl}_2$  (20ml). The mixture was kept cold for 1.5h then left for 2.5h at rt, concentrated. TFA was removed by repeated concentrations of  $\text{CH}_2\text{Cl}_2$ /ether and ether solutions of the residue.

- 5 Finally trituration of the residue with ether afforded **212e** 3.05g (85%) of a white glassy solid: mp 118-126 °C;  $[\alpha]_{\text{D}}^{24}$  -70.5 ° (c 0.1,  $\text{CH}_2\text{Cl}_2$ ). IR (KBr) 3361, 2943, 1737, 1659, 1537, 1426, 1220, 1174;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.80 (2H, m), 7.54-7.33 (4H, m), 8.83 (brs),  
10 5.44 (1H, m), 5.26-5.13 (1H, m), 4.66 (1H, m), 3.59-3.41 (1H, m), 2.97, 2.76 (2H, 2m), 2.36 (2H, m), 1.98 (2H, m), 1.75 (2H, m). MS( $\text{ES}^-$ , m/z) 344 ( $\text{M}^-$  - 1, 100%).

- (1*S*,9*S*) 6,10-Dioxo-9(fluoren-9-ylmethyloxycarbonylamino)-1,2,3,4,7,8,9,10-octahydro-  
15 6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxylic acid (**212f**), was prepared from **211f** in 96% yield by the same method as for **212e**: mp 120-126 °C;  $[\alpha]_{\text{D}}^{25}$  -72.5 ° (c 0.1,  $\text{CH}_2\text{Cl}_2$ ). IR (KBr) 3406, 2950, 1725, 1670, 1526, 1449, 1421, 1272, 1248, 1223, 1175, 761, 741;  
20  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.76 (2H, m), 7.62-7.26 (4H, m), 6.07, 5.76 (2H, brs, d, d,  $J$  = 2.9), 5.46, 5.36 (1H, 2m), 4.79-4.54 (2H, m), 4.77 (2H, m), 4.21 (1H, m), 3.41 (1H, m), 2.89 (1H, m), 2.69 (1H, m), 2.35 (2H, m), 1.98, 1.73 (4H, 2m). MS( $\text{ES}^-$ , m/z) 462 ( $\text{M}^+$  - 1, 50%),  
25 240 (100%).

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(213) (c)  $R^1 = \text{MeCO}$   
 (e)  $R^1 = \text{PhCO}$

(214) (c)  $R^1 = \text{MeCO}$   
 (e)  $R^1 = \text{PhCO}$

[2*RS*,3*S*(1*S*,9*S*)] N-(2-Benzoyloxy-5-oxotetrahydrofuran-3-yl)-9-(acetylamino)-6,10-dioxo-1,2,3,4,7,8,9,10-  
 5 octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213c), was synthesized from 212c by the same method as compound 213e to afford a mixture of diastereomers (193mg, 36%) as colourless crystals: IR (KBr) 3272, 1799, 1701, 1682, 1650, 1555, 1424, 1412, 1278, 1258, 1221, 1122, 937;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.41-7.28 (5H, m), 6.52 (0.5H, d), 6.38 (0.5H, d), 6.22 (0.5H, d), 5.57 (0.5H, d), 5.36 (0.5H, s) 5.10-5.05 (1H, m), 5.00-4.45 (5.5H, m), 3.19-2.84 (3H, m), 2.72-2.56 (1H, m), 2.51-2.25 (2H, m), 2.02 (3H, s), 1.98-1.70 (3H, m),  
 15 1.66-1.56 (3H, m); Anal. Calcd for  $\text{C}_{23}\text{H}_{28}\text{N}_4\text{O}_7$ : C, 58.47; H, 5.97; N, 11.86. Found: C, 58.37; H, 6.09; N, 11.47. MS (ES $^-$ ) 471 (M-1, 100%). Accurate mass calculated for  $\text{C}_{23}\text{H}_{29}\text{N}_4\text{O}_7$  ( $\text{MH}^+$ ): 473.2036. Found: 473.2012. Accurate mass calculated for  $\text{C}_{23}\text{H}_{28}\text{N}_4\text{O}_7\text{Na}$  ( $\text{Mna}^+$ ): 495.1856. Found: 495.1853.

[1*S*,9*S*(2*RS*,3*S*)] 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-benzoyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamide (213e). Tributyltin hydride  
 25 (2.2ml, 8.18mmol) was added dropwise to a solution of

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- acid **212e** (1.95g, 5.6mmol), (3*S*, 2*RS*) 3-allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydrofuran (Chapman, Bioorg. & Med. Chem. Lett., 2, pp. 615-618 (1992); 1.80g, 6.16mmol) and (Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub> (50mg) in dry CH<sub>2</sub>Cl<sub>2</sub> (36ml), with stirring, under dry nitrogen. After 5 min 1-hydroxybenzotriazole (1.51g, 11.2mmol 6.72mmol) was added followed after cooling (ice/H<sub>2</sub>O) by ethyldimethylaminopropyl carbodiimide hydrochloride (1.29g, 6.72mmol). After 5 mins the cooling bath was removed and the mixture was kept at room temperature for 4h, diluted with EtOAc, washed with 1M HCl, brine, sat. aq. NaHCO<sub>3</sub> and brine, dried (MgSO<sub>4</sub>) and concentrated. Flash chromatography (silica gel, 0-90% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>) gave the product as a white solid (2.34g, 78%): IR (KBr) 3499, 1792, 1658, 1536, 1421, 1279, 1257, 1123, 977, 699; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.81 (2H, m), 7.54-7.34 (8H, m), 7.1, 6.97, 6.89, 6.48 (2H, m, d, *J* 7.7, d, *J* = 7.5, d, *J* = 7.6), 5.57, 5.28 (1H, d, *J* = 5.2, s), 5.23-5.07 (2H, m), 4.93-4.42, 3.22-2.70, 2.51-2.26, 2.08-1.69, 1.22 (15H, 5m). Anal. Calcd for C<sub>28</sub>H<sub>30</sub>N<sub>4</sub>O<sub>7</sub> 0.5H<sub>2</sub>O: C, 61.87; H, 5.75; N, 10.32. Found C, 62.02; H, 5.65; N, 10.25.

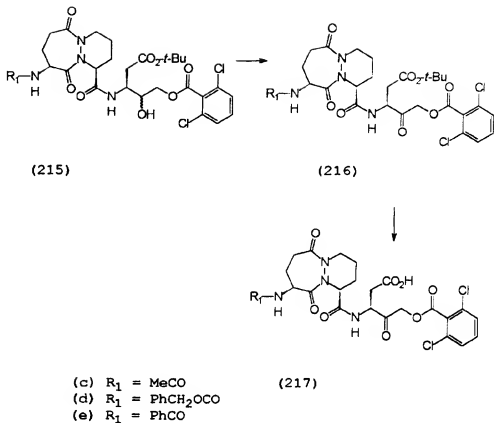
- [3*S*(1*S*,9*S*)] 3-(9-Acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-  
[1,2-*a*][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (214c), was synthesized from 213c by a method similar to the method used to synthesize 214e from 213e to provide colourless crystals (140mg, 99%): mp 90-180 °C; [α]<sub>D</sub><sup>22</sup> -114 (c 0.10, MeOH); IR (KBr) 3334, 3070, 2946, 1787, 1658, 1543, 1422, 1277, 1258; <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ 8.66 (1H, m), 8.18 (1H, d), 6.76 (1H, s), 5.08 (1H, m), 4.68 (1H, m), 4.30 (1H, m), 2.92-2.70 (2H, m),

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2.27-2.06 (3H, m), 1.95-1.72 (4H, m), 1.85 (3H, s), 1.58 (2H, m); MS (ES <sup>-</sup>) 381 (M-1, 100%); Accurate mass calculated for C<sub>16</sub>H<sub>23</sub>N<sub>4</sub>O<sub>7</sub> (MH<sup>+</sup>): 383.1567. Found: 383.1548.

- 5 [3S(1S,9S)] 3-(9-Benzoylamino-6,10-dioxo-  
1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-  
diazepine-1-carboxamido)-4-oxobutanoic acid (214e). A  
mixture of 213e (2.29g, 4.28mmol), 10% palladium on  
carbon (1.8g) and MeOH (160ml) was stirred under H<sub>2</sub> at  
10 atmospheric pressure for 6.3h. After filtering and  
concentrating the hydrogenation was repeated with fresh  
catalyst (1.8g) for 5h. After filtering and  
concentrating the residue was triturated with diethyl  
ether, filtered and washed well with ether to give 214e  
15 as a white solid (1.67g, 88%): mp 143-147 °C; [α]<sub>D</sub><sup>23</sup> -  
125 ° (c 0.2, CH<sub>3</sub>OH). IR (KBr) 3391, 1657, 1651, 1538,  
1421, 1280, 1258; <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.90 (2H, m), 7.63-  
7.46 (3H, m), 5.25 (1H, m), 5.08-4.85 (1H, m), 4.68-  
4.53 (2H, m), 4.33-4.24 (1H, m), 3.62-3.44, 3.22-3.11,  
20 2.75-2.21, 2.15-1.92, 1.73-1.66 (11H, 5m). Anal. Calcd  
for C<sub>21</sub>H<sub>24</sub>N<sub>4</sub>O<sub>7</sub> H<sub>2</sub>O: C, 54.54; H, 5.67; N, 12.11. Found  
C, 54.48; H, 5.63; N, 11.92.

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- 5 [3*S*,4*RS*(1*S*,9*S*)] *t*-Butyl 3-[9-acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino-[1,2-*a*][1,2]diazepine-1-carboxamido)-5-(2,6-dichlorobenzoyloxy)-4-hydroxypentanoate (215*c*), was synthesized from 214*c* by the same method as compound
- 10 215*e*, to afford a mixture of diastereomers as a white glassy solid (398mg, 84%): IR (KBr) 3336, 2977, 1736, 1658, 1562, 1541, 1433, 1368, 1277, 1150;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.36-7.32 (3H, m), 6.91 (1H, d), 6.30 (1H, d), 5.15-5.09 (1H, m) 5.01-4.88 (1H, m), 4.61-4.44 (2H, m), 4.37-4.08 (3H, m), 3.32-3.18 (1H, m), 3.04-2.89 (1H, m), 2.82-2.51 (4H, m), 2.39-2.29 (1H, m), 2.08-1.64 (4H, m) 2.02 (3H, s); Anal. Calcd for
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$C_{28}H_{34}N_4Cl_2O_9$ : C, 52.26; H, 5.64; N, 8.71. Found: C, 52.44; H, 5.87; N, 8.16. MS (ES<sup>-</sup>) 645/3/1 (M-1, 26%), 189 (81), 134 (100). Accurate mass calculated for  $C_{28}H_{37}N_4Cl_2O_9$  (MH<sup>+</sup>): 643.1938. Found: 643.1924.

- 5 Accurate mass calculated for  $C_{28}H_{36}N_4Cl_2O_9Na$  (MNa<sup>+</sup>) 665.1757. Found: 665.1756.

- [3*S*,4*RS*(1*S*,9*S*)] t-Butyl 3-(9-benzoyloxycarbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-5-(2,6-dichlorobenzoyloxy)-4-hydroxypentanoate (215d), was synthesized from 214d by the same method as compound 215e to afford a mixture of diastereomers (657mg, 70%) as a glassy white solid: IR (KBr) 3420, 3361, 2975, 2931, 1716, 1658, 1529, 1434, 1367, 1348, 1250, 1157, 1083, 1055; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.32 (8H, m), 7.14 (1H, d), 5.81 (1H, d), 5.15 (1H, m), 5.07 (2H, s), 4.74-4.65 (1H, m), 4.58-4.22 (4H, m), 4.15-4.06 (1H, m), 3.72 (1H, m), 3.32-3.21 (1H, m), 3.04-2.94 (1H, m), 2.69-2.52 (3H, m), 2.33-2.27 (1H, m), 1.95-1.59 (4H, m), 1.28 (9H, s); Anal. Calcd for  $C_{34}H_{40}N_4Cl_2O_{10} \cdot 0.5 H_2O$ : C, 54.70; H, 5.54; N, 7.50. Found: C, 54.98; H, 5.59; N, 7.24. MS (ES<sup>-</sup>) 737/5/3 (M-1, 22%), 193/1/89 (100). Accurate mass calculated for  $C_{34}H_{41}N_4Cl_2O_{10}$  (MH<sup>+</sup>) 735.2120. Found: 735.2181.

- 25 [3*S*,4*RS*(1*S*,9*S*)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-5-(2,6-dichlorobenzoyloxy)-4-hydroxypentanoate (215e), Tributyltin hydride (4.6ml; 11.4mmol) was added dropwise to a stirred mixture of (3*S*,4*RS*) t-Butyl (N-allyloxycarbonyl)-3-amino-5-(2,6-dichlorobenzoyloxy)-4-
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hydroxypentanoate (prepared by a method similar to the method described in Revesz et al., Tetrahedron. Lett., 35, pp. 9693-9696 (1994)) (2.64g; 5.7mmol),  $(\text{Ph}_3\text{P})_2\text{PdCl}_2$  (50mg),  $\text{CH}_2\text{Cl}_2$  (100ml) and DMF (20ml) at room temperature. The mixture was stirred for a further 10min was then 1-hydroxybenzotriazole (1.54g, 11.4mmol) was added. The mixture was cooled to 0 °C then ethyldimethylaminopropyl carbodiimide hydrochloride (1.31g; 6.84mmol) added. The mixture was kept at this temperature for 15min then at room temperature for 17h. The mixture was diluted with EtOAc (300ml), washed with 1M HCl (2x100ml), sat. aq.  $\text{NaHCO}_3$  (3x100ml) and brine (2x100ml), dried ( $\text{MgSO}_4$ ) and concentrated. The residue was purified by flash chromatography (2-5%  $(\text{MeOH}/\text{CH}_2\text{Cl}_2)$ ) to afford 3.24g (81%) of **215e** as a glassy solid: mp 106-110 °C; IR (KBr) 3354, 1737, 1659, 1531, 1433, 1276, 1150;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.80 (2H, dd,  $J = 7.9$  and  $1.5$ ), 7.75-7.26 (6H, m), 7.14-6.76 (2H, m), 5.30-5.02 (2H, m), 4.63-4.11 (5H, m), 3.44-3.26 (2H, m), 3.10-2.30 (5H, m), 2.10-1.60 (5H, m), 1.44 (9H, s); Anal. Calcd for  $\text{C}_{33}\text{H}_{38}\text{Cl}_2\text{N}_4\text{O}_9$ .  $0.75\text{H}_2\text{O}$ : C, 55.12; H, 5.54; N, 7.79; Cl, 9.86. Found: C, 55.04; H, 5.34; N, 7.80; Cl, 10.24. MS (ES +) 709/7/5 ( $M + 1$ ), 378 (59), 324 (64), 322 (100).

[3*S*(1*S*,9*S*)] *t*-Butyl 3-(9-acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino[1,2-*a*][1,2]-diazepine-1-carboxamido)-5-(2,6-dichlorobenzoyloxy)-4-oxopentanoate (**216c**), was synthesized from **215c** by the same method as compound **216e** as a glassy white solid (300mg, 83%): mp 80-125 °C;  $[\alpha]_D^{23}$  -89.1 ( $c$  1.08,  $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3356, 2979, 2935, 1740, 1659, 1532,

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1434, 1369, 1276, 1260, 1151;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.39-7.32 (3H, m), 7.13 (1H, d), 6.34 (1H, d), 5.22-5.17 (1H, m), 5.11 (1H, d), 5.04 (1H, d), 4.99-4.88 (2H, m), 4.64-4.52 (1H, m), 3.29-3.11 (1H, m), 3.05-2.67 (4H, m), 2.39-2.29 (1H, m), 2.02 (3H, s), 1.98-1.75 (4H, m), 1.46 (9H, s); Anal. Calcd for  $\text{C}_{28}\text{H}_{34}\text{N}_4\text{Cl}_2\text{O}_9$ : C, 52.42; H, 5.34; N, 8.73. Found: C, 52.53; H, 5.70; N, 7.85. MS (ES $^-$ ) 643/41/39 (M-1, 100%). Accurate mass calculated for  $\text{C}_{28}\text{H}_{35}\text{N}_4\text{Cl}_2\text{O}_9$  ( $\text{MH}^+$ ): 641.1781. Found: 641.1735. Accurate mass calculated for  $\text{C}_{28}\text{H}_{34}\text{N}_4\text{Cl}_2\text{O}_9\text{Na}$  ( $\text{Mna}^+$ ): 663.1601. Found: 663.1542.

[3S(1S,9S)] t-Butyl 3-(9-benzyloxycarbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-5-(2,6-dichlorobenzoyloxy)-4-oxopentanoate (216d), was synthesized from 215d by the same method as compound 216e to afford 216d as a white glassy solid (688mg, 68%): mp 90-170  $^\circ\text{C}$ ;  $[\alpha]_{\text{D}}^{25}$  -83.4 (c 1.01,  $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3338, 2933, 1736, 1670, 1525, 1433, 1417, 1368, 1258, 1151, 1056, 1031;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.33 (8H, m), 7.18 (1H, d), 5.65 (1H, d), 5.19 (1H, m), 5.09 (2H, s), 4.98-4.86 (1H, m), 4.82-4.49 (2H, d), 3.30-3.07 (1H, m), 3.05-2.59 (4H, m), 2.42-2.27 (1H, m), 2.16-1.59 (5H, m), 1.42 (9H, s); MS (ES $^-$ ) 737/5/3 (M, 13+, 185 (100).

[3S(1S,9S)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-5-(2,6-dichlorobenzoyloxy)-4-oxopentanoate (216e). Dess-Martin reagent (3.82g; 9.0mmol) was added to a stirred solution of the alcohol 215e (3.17g; 4.5mmol) in

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- CH<sub>2</sub>Cl<sub>2</sub> (100ml). The mixture was stirred for 1h, diluted with EtOAc (300ml), then washed with a 1:1 mixture of sat. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and sat. NaHCO<sub>3</sub> (100ml) followed by brine (100ml). The mixture was dried (MgSO<sub>4</sub>) then concentrated. The residue was purified by flash chromatography to afford 2.2g (70%) of **216e** as a colourless solid: mp 102-107 °C; [α]<sub>D</sub><sup>32</sup> -82.5 (c 0.1, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3374, 2937, 1739, 1661, 1525, 1433, 1275, 1260, 1152; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.85-7.78 (2H, m), 7.57-7.32 (6H, m), 7.09 (1H, d, J = 7.9), 7.01 (1H, d, J 7.3), 5.25-5.16 (1H, m), 5.16-5.05 (1H, m), 5.15 (1H, d), 5.03 (1H, d), 4.99-4.90 (1H, m), 4.68-4.54 (1H, m), 3.31-3.17 (1H, m), 3.17-2.72 (4H, m), 2.45-2.35 (1H, m), 2.30-1.66 (5H, m), 1.44 (9H, s); Anal. Calcd for C<sub>33</sub>H<sub>36</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>9</sub> · 0.5H<sub>2</sub>O: C, 55.62; H, 5.23; N, 7.86; Cl, 9.95. Found: C, 55.79; H, 5.15; N, 7.80; Cl 9.81. MS (ES +) 729/7/5 (M + Na), 707/5/3 (M + 1), 163 (100%).

- [3*S*(1*S*,9*S*)] 3-(9-Acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-*a*][1,2]diazepine-1-carboxamido)-5-(2,6-dichlorobenzoyloxy)-4-oxopentanoic acid (**217c**), was synthesized from **216c** by the same method as compound **217e** as a glassy white solid (166mg, 66%): mp 85-175 °C; [α]<sub>D</sub><sup>25</sup> -156 (c 0.13, MeOH); IR (KBr) 3373, 2929, 1742, 1659, 1562, 1533, 1433, 1412, 1274, 1266, 1223, 1197, 1145, 1138; <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.38 (3H, s), 5.14-5.03 (1H, m), 4.49-4.32 (2H, m), 3.50-3.27 (1H, m), 3.11-2.92 (1H, m), 2.84-2.62 (2H, m), 2.46-2.11 (2H, m), 2.05-1.46 (5H, m), 1.92 (3H, s); Anal. Calcd for C<sub>24</sub>H<sub>26</sub>N<sub>4</sub>Cl<sub>2</sub>O<sub>9</sub> · H<sub>2</sub>O: C, 47.77; H, 4.68; N, 9.29. Found: C, 47.75; H, 4.59; N, 9.07. MS (ES +) 627/5/3 (M-K, 21%), 611/9/7 (M+Na, 87), 589/7/5 (M<sup>+</sup> +1, 71),

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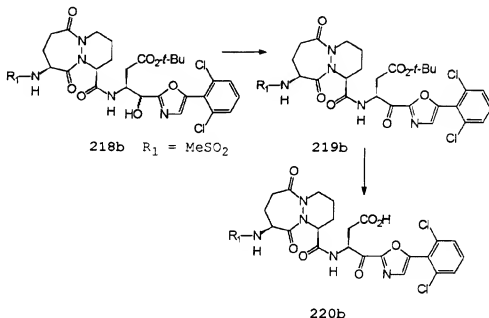
266 (100); Accurate mass calculated for  $C_{24}H_{27}N_4Cl_2O_9$  ( $MH^+$ ): 585.1155. Found: 585.1134.

[3S(1S,9S)] 3-(9-Benzoyloxycarbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-(2,6-dichlorobenzoyloxy)-4-oxopentanoic acid (217d), was synthesized from 216d by the same method as compound 217e to afford 217d as a white glassy solid (310mg, 96%): mp 85-110 °C;  $[\alpha]_D^{24}$  -85.9 (c 0.13, MeOH); IR (KBr) 3351, 2945, 1738, 1669, 1524, 1433, 1258, 1147, 1057;  $^1H$  NMR ( $CD_3OD$ )  $\delta$  7.56 (4H, m), 7.45 (5H, m), 5.32 (2H, m), 5.20 (2H, s), 4.76-4.48 (3H, m), 3.65-3.38 (3H, m), 3.27-3.09 (2H, m), 3.03-2.89 (2H, m), 2.65-2.24 (3H, m), 2.19-1.62 (5H, m); MS (ES -) 679/7/5 (M-1, 100%); Accurate mass calculated for  $C_{30}H_{31}N_4Cl_2O_{10}$  ( $MH^+$ ): 677.1417. Found: 677.1430.

[3S(1S,9S)] 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-(2,6-dichlorobenzoyloxy)-4-oxopentanoic acid (217e), TFA (25ml) was added dropwise to an ice cold stirred solution of the ester 216e (2.11g, 3.0mmol). The mixture was stirred at 0 °C for 20min then at room temperature for 1h. The mixture was evaporated to dryness then coevaporated with ether three times. Addition of dry ether (50 ml) and filtration afforded 1.9g (98%) of 217e as a colourless solid: mp 126-130 °C;  $[\alpha]_D^{30}$  -122.0 (c 0.1, MeOH); IR (KBr) 3322, 1740, 1658, 1651, 1532, 1433, 1277, 1150;  $^1H$  NMR ( $D_6$ -DMSO)  $\delta$  8.87 (1H, d,  $J$  = 7.4), 8.61 (1H, d,  $J$  = 7.8), 7.92-7.86 (2H, m), 7.65-7.43 (6H, m), 5.25-5.12 (3H, m), 4.94-4.60 (2H, m), 4.44-4.22 (1H, m),

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3.43-3.10 (1H, m), 3.00-2.52 (3H, m), 2.45-2.10 (3H, m), 2.10-1.75 (2H, m), 1.75-1.50 (2H, m); Anal. Calcd for  $C_{29}H_{28}Cl_2N_4O_9 \cdot 1H_2O$ : C, 52.34; H, 4.54; N, 8.42; Cl, 10.66. Found: C, 52.02; H, 4.36; N, 8.12; Cl, 10.36. MS (ES<sup>-</sup>) 649/7/5 (M - 1), 411 (100%).



[3*S*,4*RS*(1*S*,9*S*)] *t*-Butyl 4-[5-(2,6-dichlorophenyl)-oxazol-2-yl]-3-(6,10-dioxo-9-methylsulphonylamino-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino-[1,2-*a*][1,2]diazepine-1-carboxamido)-4-hydroxybutanoate (218b), was prepared from the acid 212b and 99 in an analogous way to compound 215e to afford a mixture of diastereomers (865mg, 80%) as a colourless solid: IR (KBr) 3296, 2974, 1723, 1659, 1544, 1518, 1430, 1394, 1370, 1328, 1273, 1256, 1156, 1134; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.45-7.28 (4H, m), 7.26-7.15 (2H, m), 5.26-5.10 (2H, m), 4.80-4.67 (1H, m), 4.59-4.42 (2H, m), 3.32-3.17 (1H, m), 2.96 (3H, 2xs), 2.93-2.79 (1H, m), 2.71-2.53

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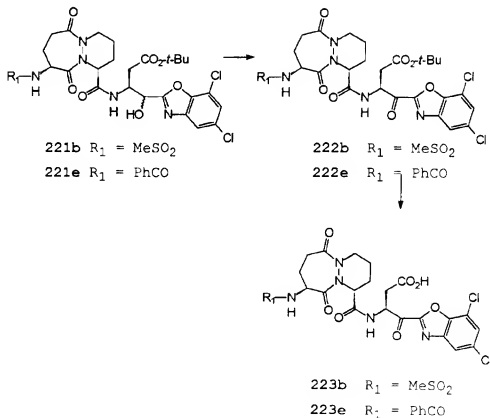
(4H, m), 2.38-2.28 (1H, m), 2.07-1.81 (4H, m); Anal. Calcd for  $C_{28}H_{35}N_5Cl_2O_9S$ . 0.5  $H_2O$ : C, 48.21; H, 5.20; N, 10.03. Found: C, 48.35; H, 5.26; N, 9.48. MS (ES +) 714/2/0 ( $M + Na$ , 25%), 692/90/88 ( $M^+ + 1$ , 51%),  
5 636/4/2 (38), 246 (100). Accurate mass calculated for  $C_{28}H_{36}N_5Cl_2O_9S$  ( $MH^+$ ): 688.1611. Found: 688.1615.

[3*S*(1*S*,9*S*)]*t*-Butyl 4-[5-(2,6-dichlorophenyl)-oxazol-2-yl]-3-(6,10-dioxo-9-methylsulphonylamino-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-4-oxobutanoate (219b), was  
10 prepared from 218b in an analogous way to compound 216e as an off-white powder (675mg, 81%): mp 100-200 °C;  $[\alpha]_D^{24}$  -84.9 (c 1.01,  $CH_2Cl_2$ ); IR (KBr) 3336, 2978, 2936, 1719, 1674, 1510, 1433, 1421, 1369, 1329, 1274,  
15 1257, 1155, 991, 789;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.47-7.38 (4H, m), 7.24 (1H, d), 5.61-5.53 (1H, m), 5.48 (1H, d), 5.38-5.30 (1H, m), 4.67-4.45 (2H, m), 3.48-3.18 (2H, m), 3.04-2.90 (2H, m), 2.97 (3H, s), 2.69-2.54 (1H, m), 2.42-2.32 (1H, m), 2.22-2.15 (1H, m), 2.07-1.93 (3H,  
20 m), 1.71-1.65 (2H, m), 1.38 (9H, s); Anal. Calcd for  $C_{28}H_{33}N_3Cl_2O_9S$ : C, 48.98; H, 4.84; N, 10.20; S, 4.67. Found: C, 48.73; H, 4.95; N, 9.65; S, 4.54. MS (ES +) 692/90/88 ( $M^+ + 1$ , 100%), 636/4/2 (71). Accurate mass calculated for  $C_{28}H_{34}N_5Cl_2O_9S$  ( $MH^+$ ): 686.1454. Found:  
25 686.1474.

[3*S*(1*S*,9*S*)] 4-[5-(2,6-Dichlorophenyl)oxazol-2-yl]-3-(6,10-dioxo-9-methylsulphonylamino-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (220b), was prepared  
30 from 219b in an analogous way to compound 217e as a pale cream powder (396mg, 87%): mp 100-200 °C;  $[\alpha]_D^{27}$  -

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129 (c 0.12, MeOH); IR (KBr) 3310, 3153, 1713, 1667, 1557, 1510, 1432, 1421, 1329, 1273, 1258, 1221, 1193, 1153, 1134, 992, 789;  $^1\text{H}$  NMR ( $d^6$  DMSO)  $\delta$  7.88 (1H, s), 7.81-7.60 (4H, m), 5.49-5.28 (1H, m), 5.24-5.14 (1H, m), 4.46-4.22 (2H, m), 3.30-3.03 (2H, m), 2.97-2.76 (3H, m), 2.96 (3H, s), 2.46-2.24 (1H, m), 2.16-2.05 (1H, m), 2.03-1.78 (3H, m), 1.68-1.46 (2H, m); MS (ES-) 632/30/28 (M - 1, 68%), 149/7/5 (100). Accurate mass calculated for  $\text{C}_{24}\text{H}_{26}\text{N}_5\text{Cl}_2\text{O}_9\text{S}$  ( $\text{MH}^+$ ): 630.0828. Found: 630.0852.



15 [3S,4RS(1S,9S)] t-Butyl 4-(5,7-dichlorobenzoxazol-2-yl)-3-(6,10-dioxo-9-methylsulfonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-

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[1,2-a][1,2]diazepine-1-carboxamido)-4-hydroxybutanoate (221b), was prepared from the acid 212b and (3S,4RS) t-butyl N-(allyloxycarbonyl)-3-amino-4-hydroxy-4-(5,7-dichlorobenzoxazol-2-yl)butanoate (204) by an analogous method as that used for compound 215e to afford a mixture of diastereomers (460mg, 70%) as a glass: IR (film) 3325, 1725, 1664, 1453, 1399, 1373, 1327, 1274, 1256, 1155; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.57 (1H, m), 7.36 (2H, m), 6.06 (1H, t), 5.29 (2H, m), 4.79 (1H, m), 4.47 (1H, m), 3.23 (1H, m), 2.97 and 2.94 (3H combined, 2 x s), 2.9-2.4 (4H, m), 2.30 (1H, m), 1.96 (4H, m), 1.41 and 1.37 (9H combined, 2 x s). MS ES Da/e 660 (M - 1)<sup>-</sup> Cl<sup>35</sup> 100%, 662 (M - 1)<sup>-</sup> Cl<sup>37</sup>.

[3S,4RS(1S,9S)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-4-(5,7-dichlorobenzoxazol-2-yl)-4-hydroxybutanoate (221e), was prepared from the acid (212e) and (3S,4RS) t-butyl N-(allyloxycarbonyl)-3-amino-4-hydroxy-4-(5,7-dichlorobenzoxazol-2-yl)butanoate (204) by an analogous method as that used for compound 215e to afford a mixture of diastereomers (613mg, 87%) as a glass: IR (film) 3328, 1729, 1660, 1534, 1454, 1422, 1399, 1276, 1254, 1155; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.80 (2H, d), 7.60-7.35 (5H, m), 7.05 (2H, m), 5.13 (3H, m), 4.74 (1H, m), 4.51 (1H, m), 3.25 (1H, m), 3.1-2.6 (5H, m), 2.33 (1H, m), 2.1-1.5 (5H, m), 1.43 and 1.41 (9H combined, 2 x s). MS ES<sup>+</sup> Da/e 688 (M + 1)<sup>+</sup> Cl<sup>35</sup> 55%, 690 (M + 1)<sup>+</sup> Cl<sup>37</sup> 35%, 328 100%.

[3S(1S,9S)] t-Butyl 4-(5,7-dichlorobenzoxazol-2-yl)-3-(6,10-dioxo-9-methylsulphonylamino-1,2,3,4,7,8,9,10-



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octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoate (222b), was prepared from 221b by an analogous method as that used for compound 216e to afford a colourless glass (371mg, 86%):  $[\alpha]_D^{26}$  -81.0 (c 0.1, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3324, 2979, 2936, 1726, 1664, 1394, 1370, 1328, 1155, 991; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.78 (1H, d), 7.57 (2H, m), 5.87 (1H, d), 5.69 (1H, m), 5.47 (1H, m), 4.55 (2H, m), 3.24 (2H, m), 3.0 (5H, m + s), 2.59 (1H, m), 2.39 (1H, m), 2.2 - 1.7 (4H, m), 1.65 (1H, m), 1.40 (9H, s).

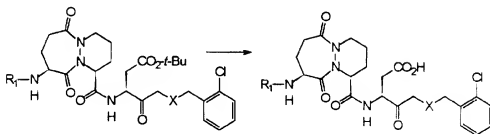
[3S(1S,9S)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-4-(5,7-dichlorobenzoxazol-2-yl)-4-oxobutanoate (222e), was prepared from 221e by an analogous method as that used for compound 216e to afford a colourless glass (480mg, 84%):  $[\alpha]_D^{25}$  -86.4 ° (c 0.1 CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3337, 2978, 2938, 1728, 1657, 1534, 1456, 1422, 1395, 1370, 1277, 1250, 1154; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.80 (3H, m), 7.50 (4H, m), 7.20 (1H, d), 7.02 (1H, d), 5.60 (1H, m), 5.28 (1H, m), 5.15 (1H, m), 4.11 (1H, m), 3.34 (2H, m), 2.96 (3H, m), 2.40 (1H, m), 2.20 (1H, m), 1.92 (2H, m), 1.67 (2H, m), 1.38 (9H, s). MS ES<sup>-</sup> Da/e 684 (M - 1)<sup>-</sup> Cl<sup>35</sup> 47%, 686 (M - 1)<sup>-</sup> Cl<sup>37</sup> 32%.

[3S(1S,9S)] 4-(5,7-Dichlorobenzoxazol-2-yl)-3-(6,10-dioxo-9-methylsulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (223b), was prepared from 222b by an analogous method as that used for compound 217e to afford an off-white solid (257mg, 78%):  $[\alpha]_D^{25}$  -105.7 ° (c 0.1, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3321,

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1723, 1663, 1407, 1325, 1151, 992;  $^1\text{H}$  NMR ( $\text{D}_6\text{-DMSO}$ )  $\delta$  8.96 (1H, d), 8.18 (1H, d), 7.96 (1H, d), 5.50 (1H, m), 5.15 (1H, m), 4.30 (2H, m), 3.06 (2H, m), 2.87 (5H, m + s), 2.29 (1H, m), 1.99 (4H, m), 1.56 (2H, m).

- 5 [3*S*(1*S*,9*S*)] 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-(5,7-dichlorobenzoxazol-2-yl)-4-oxobutanoic acid (223e), was prepared from 222e by an analogous method as that used  
 10 for compound 217e to afford a pale cream solid (311mg, 78%): mp 167-180 °C;  $[\alpha]_{\text{D}}^{23}$  -88.6 ° (c 0.1  $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3331, 1724, 1658, 1534, 1458, 1421, 1279, 1256, 991;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.77 (4H, m), 7.4 (5H, m), 5.57 (1H, bs), 5.33 (1H, bs), 5.47 (1H, q), 4.56 (1H, bd),  
 15 3.60 (2H, m), 3.20 (3H, m), 2.76 (1H, m), 2.36 (1H, dd), 2.0 (3H, m), 1.66 (1H, m). MS ES  $\text{Da/e}$  628 ( $\text{M} - 1$ ) $^-$   $\text{Cl}^{35}$  7%, 630 ( $\text{M} - 1$ ) $^-$   $\text{Cl}^{37}$  2.3%, 584 100%.

224e  $\text{R}_1 = \text{PhCO}$ ,  $\text{X} = \text{S}$ 226e  $\text{R}_1 = \text{PhCO}$ ,  $\text{X} = \text{S}$ 225e  $\text{R}_1 = \text{PhCO}$ ,  $\text{X} = \text{C}$ 227e  $\text{R}_1 = \text{PhCO}$ ,  $\text{X} = \text{C}$ 

- 20 [3*S*(1*S*,9*S*)] *t*-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-(2-chlorophenyl)methylthio-4-oxopentanoate (224e). 1-Hydroxybenzotriazole (0.23g,

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1.71mmol) and ethyl dimethylaminopropyl carbodiimide hydrochloride was added to a stirred solution of the acid **212e** (0.295g, 0.853mmol) in THF (5ml). After 5min water (0.5ml) was added followed, after a further 7min, by the addition of a solution of (3S) t-butyl-3-allyloxycarbonylamino-5-(2-chloro-phenyl)methylthio-4-oxopentanoate (**123**, 0.478g, 1.02mmol) and  $(PPh_3)_2PdCl_2$  (20mg) in THF (2ml). Tributyltin hydride (0.65ml, 2.33mmol) was added dropwise during 20min. The mixture was kept for 4.5h then diluted with EtOAc, washed with 1M HCl, brine, sat. aq.  $NaHCO_3$  and then brine again. The mixture was dried ( $MgSO_4$ ) and concentrated. The residue was triturated several times with hexane, which was decanted and discarded, then purified by flash chromatography (10-100% EtOAc in  $CH_2Cl_2$ ) to afford 0.2g (35%) of a white glassy solid: mp 70-72 °C;  $[\alpha]_D^{26}$  - 82.5 ° (c 0.02,  $CH_2Cl_2$ ). IR (KBr) 3404, 1726, 1660, 1534, 1524, 1422, 1277, 1254, 1154;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.83-7.78 (2H, m), 7.7, 7.75-7.32, 7.26-7.20 (7H, 3m), 7.12 (1H, d,  $J$  = 8.2), 7.01 (1H, d,  $J$  = 7.3), 5.23-5.08 (2H, m), 5.03-4.94 (1H, m), 4.62 (1H, dt,  $J$  = 14.5), 3.78 (2H, m), 3.38-3.29 (1H, m), 3.26 (2H, s), 3.06-2.82 (4H, m), 2.71 (1H, dd,  $J$  = 17.2, 4.5), 2.39 (1H, dd,  $J$  = 13.2, 6.5), 2.15-1.83, 1.73-1.63 (5H, m), 1.45 (9H, s). Anal. Calcd for  $C_{33}H_{39}ClN_4O_7S$ : C, 59.05; H, 5.86; N, 8.35. Found: C, 59.00; H, 5.80; N, 7.92.

[3*RS*, (1*S*,9*S*)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-(2-chlorophenylmethyloxy)-4-oxopentanoate (**225e**), was prepared from acid **212e** and (3S) t-butyl N-(allyloxycarbonyl)-3-amino-5-(2-chlorophenylmethyloxy)-4-oxopentanoate (**201**) using a

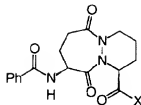
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method similar to that used for compound 224e, to afford 40mg (23%) of a glassy solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.83-7.73 (2H, m), 7.67-7.10 (9H, m), 5.23-5.09 (2H, m), 4.59 (1H, m), 4.45-4.22 (2H, m), 3.7-3.19, 3.08-2.72, 2.71-2.47, 2.05-1.85, 1.72-1.61, 1.45-1.26 (20H, 6m).

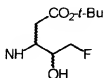
[3S(1S,9S)] 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-(2-chlorophenyl)methylthio-4-oxopentanoic acid (226e), was prepared from 224e by an analogous method as that used for compound 217e which afforded 0.22g (81%) of an off-white solid: mp 95-100 °C;  $[\alpha]_D^{23}$  -95.6 ° (c 0.2,  $\text{CH}_2\text{Cl}_2$ ). IR (KBr) 3393, 1720, 1658, 1529, 1422, 1279;  $^1\text{H}$  NMR ( $\text{D}_6$ -DMSO)  $\delta$  8.80 (1H, d,  $J$  = 7.5), 7.89 (2H, m), 7.7 (1H, d,  $J$  = 7.7), 7.56-7.28 (7H, m), 5.10 (1H, m), 4.87-4.73 (2H, m), 4.39 (1H, m), 3.77 (2H, m), 3.44, 3.35 (2H,  $+\text{H}_2\text{O}$ , 2m), 2.97-2.56, 2.2, 1.92, 1.61 (11H, 4m). Anal. Calcd for  $\text{C}_{29}\text{H}_{31}\text{ClN}_4\text{O}_7\text{S} \cdot 0.5\text{H}_2\text{O}$ : C, 55.02; H, 5.10; N, 8.85. Found: C, 55.00; H, 5.09; N, 8.71.

[3RS, (1S,9S)] 3-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-(2-chlorophenylmethyloxy)-4-oxopentanoic acid (227e), was prepared from 225e by an analogous method as that used for compound 217e. The product was further purified by flash chromatography (0-5% MeOH/ $\text{CH}_2\text{Cl}_2$ ) to afford 19mg (81%) of a glassy solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.79 (2H, m), 7.66-7.18 (9H, m), 5.30-5.10 (2H, m), 4.85 (1H, m), 4.65 (2H, m), 4.53 (1H, m), 4.28 (2H, m), 3.28, 3.01, 2.72, 2.33, 1.94, 1.60 (11H, 6m). MS ( $\text{ES}^-$ ,  $m/z$ ) 597 ( $\text{M}^+ - 1$ , 100%).

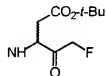
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228e X =



229e X =



230e X =



- [3*RS*,4*RS*(1*S*,9*S*)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-  
 5 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-  
 [1,2-a][1,2]-diazepine-1-carboxamido)-5-fluoro-4-  
 (228e). 1-Hydroxybenzotriazole (0.23g, 1.68mmol,  
 followed by ethyldimethylaminopropyl carbodiimide  
 hydrochloride (0.21g, 1.09mmol) were added to a stirred  
 10 solution of the acid 212e (0.29g, 0.84mmol) in CH<sub>2</sub>Cl<sub>2</sub>  
 (3ml) at rt. The mixture was kept for 10min then a  
 solution of (3*RS*,4*RS*) t-butyl 3-amino-5-fluoro-4-  
 hydroxypentanoate (Revesz, L. et al. Tetrahedron Lett.,  
 52, pp. 9693-9696 (1994); 0.29g, 1.40mmol) in CH<sub>2</sub>Cl<sub>2</sub>  
 15 (3ml) was added followed by 4-dimethylaminopyridine

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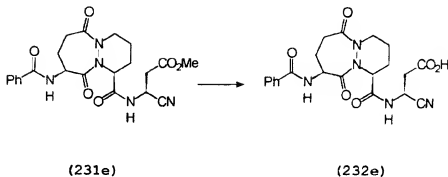
(10mg). The solution was stirred for 17h, diluted with EtOAc, washed with 1M HCl, brine, sat. aq. NaHCO<sub>3</sub> and brine again, dried (MgSO<sub>4</sub>) and concentrated. The residue was purified by flash chromatography (50-100% EtOAc/CH<sub>2</sub>Cl<sub>2</sub> and 5% MeOH/EtOAc) to afford 0.25g (56%) of a white glassy solid: IR (KBr) 3343, 1726, 1658, 1536, 1426, 1279, 1257, 1157; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.84-7.79 (2H, m), 7.57-7.40 (3H, m), 7.05-6.92, 6.73 (2H, 2m), 5.17-5.04 (2H, m), 4.56, 4.35-4.21, 4.04 (5H, 3m), 3.36, 3.09-2.34, 2.00 (11H, 3m), 1.46 (9H, s). Anal. Calcd for C<sub>26</sub>H<sub>35</sub>N<sub>4</sub>O<sub>7</sub> · 0.5H<sub>2</sub>O: C, 57.45; H, 6.65; N, 10.31. Found: C, 57.64; H, 6.56; N, 10.15.

[3*RS*,4*RS*(1*S*,9*S*)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]-diazepine-1-carboxamido)-5-fluoro-4-oxypentanoate (229e) was prepared from 228c by an analogous method to that used for compound 216e. After purification by flash chromatography (30-50% EtOAc/CH<sub>2</sub>Cl<sub>2</sub>) the product was obtained as a white glassy solid (0.194g, 89%): IR (KBr) 3376, 1728, 1659, 1529, 1424, 1279, 1256, 1156.

[3*RS*, (1*S*,9*S*)] 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-fluoro-4-oxopentanoic acid (230e), was prepared from 229e by an analogous method to that used for compound 217e to afford 230e as a white glassy solid (100%): mp 105-125 °C; [α]<sub>D</sub><sup>23</sup> -91.4 ° (c 0.72, CH<sub>3</sub>OH). IR (KBr) 3336, 1789, 1737, 1659, 1535, 1426, 1279, 1258, 1186; <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.71-7.68 (2H, m), 7.37-7.23 (3H, m), 5.02, 4.88-4.63,

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4.37-4.0 (6H, 3m), 3.30, 2.97, 2.68-2.60, 2.37-1.54 (11H, 4m). MS(ES<sup>-</sup>, m/z) 475 (M<sup>+</sup> - 1, 100%).



- [3S(1S,9S)]-Methyl 9-(benzoylamino)-3-[6,10-dioxo-  
 5 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-  
 [1,2-a][1,2]diazepine-1-carboxamido]-3-cyanopropanoate  
 (231e). N-Fluorenylmethyloxy-carbonyl-3-amino-3-  
 cyanopropionic acid methyl ester (EP0547699A1, 385mg,  
 1.1mmol) was treated with 17ml of diethylamine. After  
 10 1.5h stirring at room temperature the solution was  
 concentrated. The residue was chromatographed on  
 silica gel (3% methanol in CH<sub>2</sub>Cl<sub>2</sub>) and gave the free  
 amine as a pale yellow oil. To a solution of this oil  
 and hydroxybenzotriazole (297mg, 2.19mmol) in DMF  
 15 (5ml), was added at 0 °C ethyldimethylaminopropyl  
 carbodiimide (232mg, 1.21mmol, 1.1 equiv) followed by  
 (1S,9S) 9-(benzoylamino)-[6,10-dioxo-1,2,3,4,7,8,9,10-  
 octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-  
 carboxylic acid (212e). After stirring at 0 °C for 5  
 20 min and then at room temperature overnight, the mixture  
 was diluted with CH<sub>2</sub>Cl<sub>2</sub> (50ml) and the resulting  
 solution washed successively with 1M HCl (2 x 30ml),  
 H<sub>2</sub>O (30ml), 10% NaHCO<sub>3</sub> (2 x 30ml) and sat. aq. NaCl,  
 dried (MgSO<sub>4</sub>) and concentrated. Purification by flash

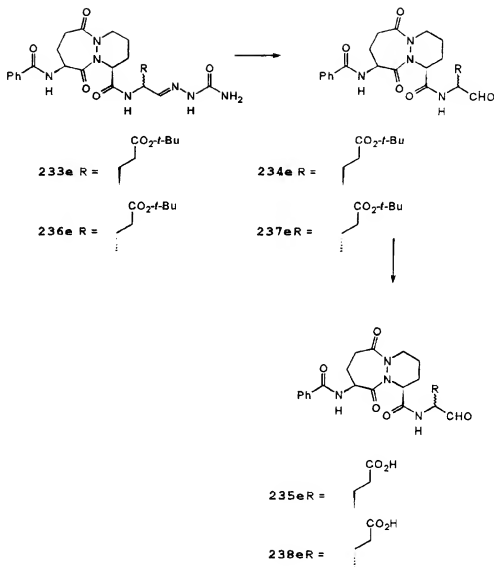
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chromatography on silica gel (3% methanol in  $\text{CH}_2\text{Cl}_2$ ) afforded the compound **231e** (404mg, 83%) as a solid:  $[\alpha]_{\text{D}}^{20} -121^\circ$  (c 0.14,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.40-7.83 (5H, m), 7.38 (1H, d), 6.96 (1H, d), 5.27-5.07 (2H, m), 4.66-4.50 (1H, m), 3.79 (3H, s), 3.23-2.73 (6H, m), 2.47-2.33 (1H, m), 2.15-1.82 (4H, m); Anal. Calcd for  $\text{C}_{22}\text{H}_{25}\text{N}_5\text{O}_6$ : C, 58.0; H, 5.53; N, 15.38. Found: C, 57.6; H, 5.6; N, 15.0.

- [3S(1S,9S)] 9-(Benzoylamino)-3-[6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido]-3-cyanopropanoic acid (232e)**. A solution of methyl ester **231e** (400mg, 0.88mmol) in methanol (30ml) and water (30ml) was cooled at  $0^\circ\text{C}$  and treated with diisopropylethylamine.
- The solution was stirred at  $0^\circ\text{C}$  for 10min and then at room temperature overnight. The heterogeneous mixture was concentrated and the solid obtained was chromatographed on silica gel (5% methanol/1% formic acid in  $\text{CH}_2\text{Cl}_2$ ) affording the free acid **232e** (170mg, 44%) as a white solid: mp  $155^\circ\text{C}$  (dec);  $[\alpha]_{\text{D}}^{20} -117^\circ$  (c 0.1, MeOH); IR (KBr) 3343, 3061, 2955, 1733, 1656, 1577, 1533, 1490, 1421, 1342, 1279, 1256, 1222, 1185, 708;  $^1\text{H}$  NMR ( $\text{D}^4\text{-MeOH}$ )  $\delta$  7.88-7.28 (5H, m), 5.20-5.03 (1H, m), 4.98-4.84 (2H, m), 4.75-4.53 (1H, m), 4.51-4.34 (1H, m), 3.45-3.22 (1H, m), 3.14-2.94 (1H, m), 3.14-2.94 (1H, m), 2.88-2.61 (2H, m), 2.53-1.50 (8H, m); Anal. Calcd for  $\text{C}_{21}\text{H}_{23}\text{N}_5\text{O}_6 \cdot 1.5\text{H}_2\text{O}$ : C, 53.84; H, 5.59; N, 14.95; O, 25.61. Found: C, 54.3; H, 5.4; N, 14.3.



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[4*S*, (1*S*,9*S*)] *t*-Butyl 4-[9-(benzoylamino)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino-[1,2-*a*][1,2]diazepine-1-carboxamido]-5-oxopentanoate semicarbazone (**233e**). A solution of (1*S*,9*S*) 6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-9-(benzoylamino)-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxylic acid (**212e**) (345mg, 1.0mmol), (4*S*) *t*-butyl N-

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- (allyloxycarbonyl)-4-amino-5-oxopentanoate semicarbazone (**208a**) (361mg, 1.1mmol, 1.1 equiv) and  $(\text{Ph}_3\text{P})_2\text{PdCl}_2$  (20mg) in  $\text{CH}_2\text{Cl}_2$  (5ml), was treated dropwise with  $n\text{-Bu}_3\text{SnH}$  (0.621ml, 2.3mmol, 2.1 equiv).
- 5 The resulting orange brown solution was stirred at 25 °C for 10min and then 1-hydroxybenzotriazole (297mg, 2.2mmol, 2 equiv) was added. The mixture was cooled to 0 °C and ethyldimethylaminopropyl carbodiimide (253mg, 1.3mmol, 1.2 equiv) added. After stirring at 0 °C for
- 10 10min and then at room temperature overnight, the mixture was diluted with EtOAc (50ml) and the resulting solution washed successively with 1M HCl (3 x 25ml), 10%  $\text{NaHCO}_3$  (3 x 25ml) and sat. aq. NaCl, dried ( $\text{MgSO}_4$ ) and concentrated. Flash chromatography on silica gel
- 15 (2-10% methanol in  $\text{CH}_2\text{Cl}_2$ ) afforded compound **233e** (280mg, 49%) as a tan solid:  $[\alpha]_{\text{D}}^{20}$  -95 (c 0.09, MeOH); IR (KBr) 3477, 3333, 2968, 2932, 1633, 1580, 1535, 1423, 1378, 1335, 1259, 1156, 1085, 709;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  9.32 (1H, s), 7.83-7.39 (6H, m), 7.11-7.09 (1H, m),
- 20 6.30-5.30 (2H, brs), 5.17-5.05 (2H, m), 4.62-4.38 (2H, m), 3.30-3.15 (1H, m), 3.13-2.65 (2H, m), 2.46-2.19 (3H, m), 2.15-1.54 (8H, m), 1.42 (9H, s).

- [**4R**, (**1S**,**9S**)] **t**-Butyl 4-[9-(benzoylamino)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-
- 25 [1,2-a][1,2]diazepine-1-carboxamido]-5-oxopentanoate semicarbazone (**236e**), was prepared by an analogous method to that used for **233e** using (**4R**) **t**-butyl *N*-allyloxycarbonyl-4-amino-5-oxo-pentanoate semicarbazone (**208b**, 435mg, 1.33mmol). The product was obtained as a
- 30 foam (542mg, 71%):  $[\alpha]_{\text{D}}^{20}$  -99 ° (c 0.19,  $\text{CHCl}_3$ ); IR (KBr) 3473, 3331, 3065, 2932, 2872, 1660, 1580, 1533, 1488, 1423, 1370, 1337, 1278, 1254, 1223, 1155, 1080,

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1024, 983, 925, 877, 846, 801, 770, 705;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  
 $\delta$  9.42 (1H, s), 7.81 (2H, d), 7.51-7.40 (4H, m), 7.06  
(1H, d), 6.50-5.50 (2H, broad s), 5.25-5.00 (2H, m),  
4.60-4.45 (2H, m), 3.15-2.85 (2H, m), 2.75-2.35 (1H,  
5 m), 2.30-1.23 (11H, m), 1.42 (9H, s).

[4S, (1S,9S)] t-Butyl 4-[9-(benzoylamino)-6,10-dioxo-  
1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-  
[1,2-a][1,2]diazepine-1-carboxamido]-5-oxopentanoate  
(234e). A solution of semicarbazone 233e (390mg,  
10 0.68mmol) in methanol (10ml) was cooled at 0 °C and  
then treated with a 38% aq. solution of formaldehyde  
(2ml) and 1M HCl (2ml). The reaction mixture was then  
stirred overnight at room temperature. The solution  
was concentrated to remove the methanol. The aq.  
15 solution was extracted with EtOAc (30ml). The organic  
solution was successively washed with 10%  $\text{NaHCO}_3$  (30ml)  
and sat. aq. NaCl (30ml), dried ( $\text{MgSO}_4$ ) and  
concentrated. Purification by flash chromatography on  
silica gel (2-5% methanol in  $\text{CH}_2\text{Cl}_2$ ) afforded 234e  
20 (179mg, 51%) as a white foam:  $[\alpha]_{\text{D}}^{20}$  -101 ° (c 0.064,  
MeOH); IR (KBr) 3346, 2976, 2934, 1730, 1657, 1535,  
1456, 1425, 1278, 1255, 1156, 708;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$   
9.56 (1H, s), 7.88-7.38 (5H, m), 7.01 and 6.92 (2H,  
2d), 5.27-5.08 (2H, m), 4.69-4.46 (1H, m), 3.50-3.27  
25 (2H, m), 3.15-2.73 (2H, m), 2.46-1.83 (10H, m), 1.45  
(9H, s).

[4R, (1S,9S)] t-Butyl 4-[9-(benzoylamino)-6,10-dioxo-  
1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-  
[1,2-a][1,2]diazepine-1-carboxamido]-5-oxopentanoate  
30 (237e), was prepared from 236e by an analogous method  
to 234e to afford a white foam (390mg, 85%):  $[\alpha]_{\text{D}}^{20}$

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-113 ° (c 0.242, CHCl<sub>3</sub>); IR (KBr) 3352, 3065, 2974, 1729, 1657, 1536, 1489, 1454, 1423, 1369, 1338, 1278, 1255, 1223, 1156, 1078, 1026, 981, 846, 709.

[4S, (1S,9S)] 4-[9-(Benzoylamino)-6,10-dioxo-

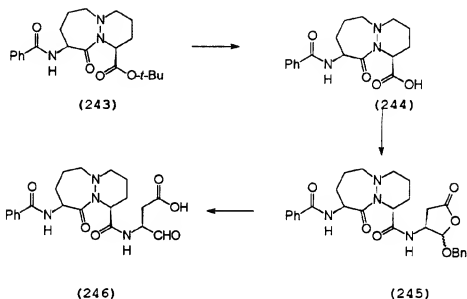
- 5 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-  
[1,2-a][1,2]diazepine-1-carboxamido]-5-oxopentanoic  
acid (235e). A solution of t-butyl ester 234e (179mg,  
0.35mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (3ml) was cooled to 0 °C and  
treated with trifluoroacetic acid (2ml). The resulting  
10 solution was stirred at 0 °C for 30min and then at room  
temperature for 2h. The solution was concentrated, the  
residue taken up in dry CH<sub>2</sub>Cl<sub>2</sub> (5ml) and the mixture  
again concentrated. This process was repeated once  
again with more CH<sub>2</sub>Cl<sub>2</sub> (5ml). The residue obtained was  
15 crystallized in diethyl ether. The precipitate was  
collected and purified on silica gel column (5%  
methanol in CH<sub>2</sub>Cl<sub>2</sub>) which afforded compound 235e as a  
white solid (111mg, 70%): mp 142 °C (dec); [α]<sub>D</sub><sup>20</sup> -85.5  
(c 0.062, MeOH); IR (KBr) 3409, 3075, 2952, 1651, 1541,  
20 1424, 1280, 1198, 1136, 717; <sup>1</sup>H NMR (D<sub>6</sub>-DMSO) δ 9.40  
(1H, s), 8.62 (2H, m), 7.96-7.38 (5H, m), 5.19-5.02  
(1H, m), 4.98-4.79 (1H, m), 4.48-4.19 (1H, m), 3.51-  
3.11 (2H, m), 3.04-2.90 (2H, m), 2.38-1.46 (10H, m).

[4R, (1S,9S)] 4-[9-(Benzoylamino)-6,10-dioxo-

- 25 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-  
[1,2-a][1,2]diazepine-1-carboxamido]-5-oxopentanoic  
acid (238e), was prepared from 237e by an analogous  
route to 235e which afforded a beige foam (190mg, 60%):  
[α]<sub>D</sub><sup>20</sup> -78 (c 0.145, MeOH); IR (KBr) 3400, 3070, 2955,  
30 2925, 2855, 1653, 1576, 1541, 1490, 1445, 1427, 1342,  
1280, 1258, 1205, 1189, 1137, 1075, 1023, 983, 930,

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878, 843, 801, 777, 722;  $^1\text{H}$  NMR ( $\text{D}_6\text{-DMSO}$ )  $\delta$  9.40 (1H, s), 8.72-8.60 (2H, m), 7.89 (2H, d), 7.56-7.44 (3H, m), 5.17 (1H, m), 4.90-4.83 (1H, m), 4.46-4.36 (1H, m), 4.20-4.15 (1H, m), 3.40-3.30 (1H, m), 2.98-2.90 (2H, m), 2.50-1.60 (10H, m).



(1*S*,9*S*) *t*-Butyl 9-benzoylamino-octahydro-10-oxo-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxylate (243),

10 was prepared from (1*S*,9*S*) *t*-butyl 9-amino-octahydro-10-oxo-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxylate (Attwood, et al. *J. Chem. Soc., Perkin 1*, pp. 1011-19 (1986)), by the method described for 211e, to afford 2.03g (86%) of a colourless foam:  $[\alpha]_{\text{D}}^{25}$  -15.9 ° (c 0.5,  $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3400, 2976, 2937, 1740, 1644, 1537, 1448, 1425, 1367, 1154;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.88-7.82 (2H, m), 7.60-7.38 (4H, m), 5.46 (1H, m), 4.98 (1H, m), 3.45 (1H, m), 3.22-2.96 (2H, m), 2.64 (1H, m), 2.43-2.27 (2H, m), 1.95 (2H, m), 1.82-1.36 (4H, m), 1.50 (9H, s); Anal. Calcd for  $\text{C}_{21}\text{H}_{29}\text{N}_3\text{O}_4 \cdot 0.25\text{H}_2\text{O}$ : C,

20

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64.35; H, 7.59; N, 10.72. Found: C, 64.57; H, 7.43; N, 10.62. MS (ES +, m/z) 388 (100%,  $M^+ + 1$ ).

(1*S*,9*S*) 9-Benzoylamino-octahydro-10-oxo-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxylic acid

- 5 (244), was prepared from (1*S*,9*S*) t-butyl 9-benzoylamino-octahydro-10-oxo-6H-pyridazino-  
[1,2-*a*][1,2]diazepine-1-carboxylate (243), by the  
method described for 212e, to afford 1.52g (89%) of a  
white powder: mp. 166-169 °C (dec);  $[\alpha]_D^{25}$  -56.4 ° (c  
10 0.5, CH<sub>3</sub>OH); IR (KBr) 3361, 2963, 2851, 1737, 1663,  
1620, 1534, 1195, 1179; <sup>1</sup>H NMR (D<sub>6</sub>-DMSO)  $\delta$  12.93 (1H,  
brs), 8.44 (1H, d, *J* = 8.4), 7.93 (2H, m), 7.54 (3H,  
m), 5.46 (1H, m), 4.87 (1H, m), 3.12 (2H, m), 2.64 (1H,  
m), 2.64 (1H, m), 2.27 (1H, m), 1.98-1.68 (7H, m), 1.40  
15 (1H, m); Anal. Calcd for C<sub>17</sub>H<sub>21</sub>N<sub>3</sub>O<sub>4</sub> · 0.25H<sub>2</sub>O: C, 60.79;  
H, 6.45; N, 12.51. Found: C, 61.07; H, 6.35; N,  
12.55. MS (ES+, m/z) 332 (58%,  $M^+ + 1$ ), 211 (100).

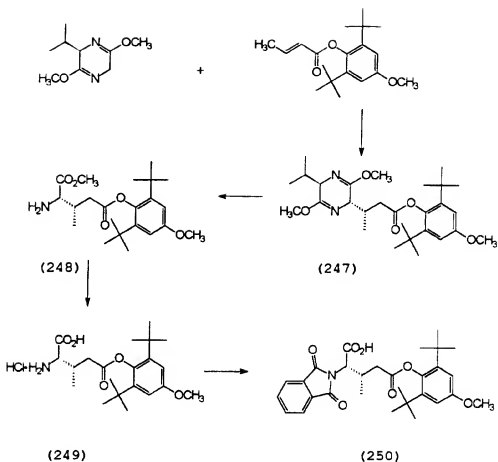
[3*S*,2*RS*(1*S*,9*S*)] N-(2-Benzoyloxy-5-oxotetrahydrofuran-3-yl)-9-benzoylamino-octahydro-10-oxo-6H-

- 20 pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide (245),  
was prepared from (1*S*,9*S*) 9-benzoylamino-octahydro-10-  
oxo-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxylic  
acid (244), by the method described for 213e, to afford  
601mg (76%) of a colourless foam: IR (KBr) 3401, 2945,  
25 1794, 1685, 1638, 1521, 1451, 1120; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$   
7.87-7.77 (2H, m), 7.57-7.14 (10H, m), 5.59-5.47 (2H,  
m), 4.97-4.32 (4H, m), 3.27-1.35 (14H, m); Anal. Calcd  
for C<sub>28</sub>H<sub>31</sub>N<sub>4</sub>O<sub>6</sub> · 0.5H<sub>2</sub>O: C, 63.50; H, 6.28; N, 10.58.  
Found: C, 63.48; H, 6.14; N, 10.52. MS (ES +, m/z)  
30 521 (100%,  $M^+ + 1$ ).

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[3*S*(1*S*,9*S*)] 3-(9-Benzoylamino-octahydro-10-oxo-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide-4-oxobutanoic acid (**246**), was prepared from [3*S*, 2*RS*(1*S*,9*S*)]N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-9-benzoylamino-octahydro-10-oxo-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide (**245**), by the method described for **214e**, to afford 396mg (84%) of a white powder: mp. 110-115 °C;  $[\alpha]_D^{26}$  -126.3 ° (c 0.2, CH<sub>3</sub>OH); IR (KBr) 3345, 2943, 1787, 1730, 1635, 1578, 1528, 1488, 1450, 1429; <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.88 (2H, m), 7.48 (3H, m), 5.55 (1H, m), 4.91 (1H, m), 4.56 (1H, m), 4.29 (1H, m), 3.41-3.05 (3H, m), 2.76-2.41 (3H, m), 2.28-2.01 (3H, m), 1.86-1.65 (4H, m), 1.36 (1H, m); Anal. Calcd for C<sub>21</sub>H<sub>26</sub>N<sub>4</sub>O<sub>6</sub> · 1.25H<sub>2</sub>O: C, 55.68; H, 6.34; N, 12.37. Found: C, 55.68; H, 6.14; N, 12.16. MS (ES<sup>+</sup>, m/z) 429 (100%, M<sup>+</sup> - 1).

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[(3*S*(2*R*, 5*S*)]-2,6-Di-*tert*-butyl-4-methoxyphenyl-3-[5-  
 (2,5-dihydro-3,6-dimethoxy-2-(1-  
 5 methylethyl)pyrazinyl)]butanoate (247). *n*-Butyllithium  
 (1.6*M* in hexane) (22.3ml, 35.7mmol) was added dropwise  
 over 20min to a solution of (2*R*)-(-)-2,5-dihydro-3,6-  
 dimethoxy-2-(1-methylethyl)pyrazine (5.8ml, 6.0g,  
 32.4mmol) in THF (250ml) cooled to -75 °C at a rate  
 10 such that the temperature was maintained below -72 °C.  
 The reaction mixture was stirred for 1h at -75 °C and a  
 solution of 2,6-di-*t*-butyl-4-methoxyphenyl-2-butenate  
 (Suzuck et al. Liebigs Ann. Chem. pp. 51-61 (1992))



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(9.9g, 32.5mmol) in THF (60ml) was added over 30 minutes maintaining the temperature below -72 °C during the addition. The reaction mixture was kept at -75 °C for 1.5h and a solution of glacial acetic acid (6ml) in THF (25ml) was added at -75 °C and the solution warmed to room temperature. The solution was poured onto 10% NH<sub>4</sub>Cl (300ml) and extracted with diethyl ether (3 x 250ml). The combined organic phases were washed with brine (2 x 200ml), dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness under reduced pressure. The residual oil was purified by flash chromatography on silica gel (20% heptane in CH<sub>2</sub>Cl<sub>2</sub>) which afforded the title compound as a light yellow oil (13.5g, 85%):  $[\alpha]_D^{20}$  -64 ° (c 0.22, MeOH); IR (KBr) 2962, 2873, 2840, 1757, 1697, 1593, 1460, 1433, 1366, 1306, 1269, 1236, 1187, 1157, 1126, 1063, 1038, 1011, 970, 924, 892, 867, 846, 831, 797, 773, 754; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 6.85 (2H, s), 4.21 (1H, t, J = 3.5), 3.98 (1H, t, J = 3.5), 3.79 (3H, s), 3.71 (3H, s), 3.69 (3H, s), 3.15 (1H, dd, J 17.8, 7.9), 2.86-2.81 (1H, m), 2.58 (1H, dd, J = 17.8, 5.9), 2.28-2.19 (1H, m), 1.33 (16H, s), 1.02 (3H, d, J = 6.8), 0.70 (6H, dd, J = 13, 6.8).

**(2S,3S)-5-[2,6-Di-*t*-butyl-4-methoxyphenyl]-1-methyl-3-methylglutamate (248).** A solution of [3S(2R, 5S)]-2,6-di-*t*-butyl-4-methoxyphenyl-3-[5-(2,5-dihydro-3,6-dimethoxy-2-(1-methylethyl)pyrazinyl)]butanoate (247) (22.4g, 45.8mmol) in acetonitrile (300ml) and 0.25N HCl (366ml, 2 equiv) was stirred at room temperature under nitrogen atmosphere for 4 days. The acetonitrile was evaporated under reduced pressure and diethylether (250ml) was added to the aq. phase. The pH of the aq. phase was adjusted to pH8-9 with concentrated ammonia

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- solution (32%) and the phases separated. The aq. phase was extracted with diethylether (2 x 250ml). The combined organic phases were dried over  $\text{Na}_2\text{SO}_4$  and evaporated to dryness under reduced pressure. The
- 5 residual oil was purified by flash chromatography on silica gel (2% methanol in  $\text{CH}_2\text{Cl}_2$ ) which afforded the required product as a light yellow oil (8.2g, 45%):  $[\alpha]_D^{20} +20^\circ$  (c 0.26, MeOH); IR(KBr) 3394, 3332, 3000, 2962, 2915, 2877, 2838, 1738, 1697, 1593, 1453, 1430, 10
- 1419, 1398, 1367, 1304, 1273, 1251, 1221, 1203, 1183, 1126, 1063, 1025, 996, 932, 891, 866, 847, 800, 772, 745;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  6.85 (2H, s), 3.79 (3H, s), 3.74 (3H, s), 3.72-3.69 (1H, m), 3.05-2.85 (1H, m), 2.67-2.50 (2H, m), 1.32 (18H, s), 0.93 (3H, d,  $J = 7$ ); Anal.
- 15 Calcd for  $\text{C}_{22}\text{H}_{35}\text{NO}_5$ : C, 67.15; H, 8.96; N, 3.56. Found: C, 67.20; H, 9.20; N, 3.70.

- (2S,3S)-5-[2,6-Di-t-butyl-4-methoxyphenyl]3-methylglutamate (249).** A solution of (2S,3S)-5-[2,6-di-t-butyl-4-methoxyphenyl]3-methylglutamate (**248**)
- 20 (8.0g, 20.3mmol) in 5N HCl (200ml) was heated at reflux for 2h. The reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in cyclohexane (x4) and evaporated to dryness (x4) which afforded a white solid (7.9g, 93%): mp  $230^\circ\text{C}$ ;  $[\alpha]_D^{20} +22^\circ$  (c 0.27, MeOH); IR (KBr) 3423, 2964, 1755, 1593, 1514, 1456, 1421, 1371, 1303, 1259, 1201, 1179, 1138, 1106, 1060, 966, 926, 861, 790, 710;  $^1\text{H}$  NMR (MeOD)  $\delta$  6.76 (2H, s), 4.02 (1H, d,  $J = 3.7$ ), 3.67 (3H, s), 3.05-2.85 (1H, m), 2.80-2.55 (2H, m), 1.22 (18H, s), 1.09 (3H, d,  $J = 6.3$ );  $^{13}\text{C}$  NMR (MeOD)  $\delta$  174.5, 171.4,
- 30 158.6, 145.2, 143.1, 113.2, 58.3, 56.3, 39.8, 36.9,

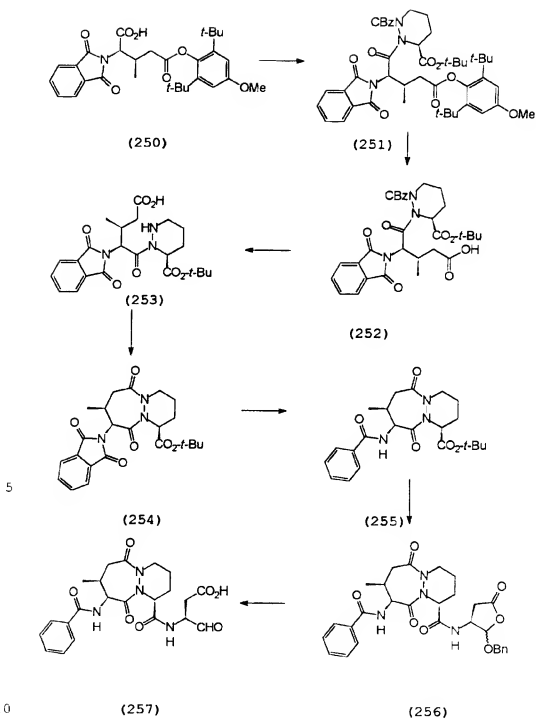
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32.5, 16.6; Anal. Calcd for  $C_{21}H_{34}ClNO_5$ : C, 60.64; H, 8.24; N, 3.37. Found: C, 60.80; H, 8.40; N, 3.40.

**(2S,3S)-5-[2,6-Di-t-butyl-4-methoxyphenyl]3-methyl-2-phthalimido-1,5-pentanedioate (250),**

- 5 Diisopropylethylamine (4.1ml, 3.04g, 23.5mmol, 1.25 equiv) and phthalic anhydride (3.5g, 23.6mmol, 1.25 equiv) were added to a solution of (2S,3S)-5-[2,6-di-t-butyl-4-methoxyphenyl]3-methylglutamate (**249**) (7.8g, 18.6mmol) in toluene (300ml). and the resulting mixture
- 10 was heated at reflux for 3 hours. After cooling to room temperature, the reaction mixture was evaporated to dryness and the resulting oil purified by flash chromatography on silica gel (2% methanol in  $CH_2Cl_2$ ) which afforded the required product as a white foam
- 15 (8.35g, 87%):  $[\alpha]_D^{20}$  -20 ° (c 1.04, MeOH); IR (KBr) 3480, 2968, 2880, 1753, 1721, 1594, 1462, 1422, 1388, 1303, 1263, 1216, 1183, 1148, 1062, 1003, 933, 899, 755, 723;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.92-7.07 (2H, m), 7.78-7.73 (2H, m), 6.84 (2H, s), 4.95 (1H, d), 3.78 (3H, s),
- 20 3.30-3.05 (2H, m), 2.85-2.65 (1H, m), 1.30 (18H, s), 1.13 (3H, d).

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1-(2,6-di-*t*-Butyl-4-methoxy)-phenyl-5-(1-benzyloxycarbonyl-3-*t*-butoxycarbonyl-hexahydro-pyridazin-2-yl)-3-methyl-4-phthalimidopentan-1,5-dioate (251). A solution of the amino acid (250) (1.2g, 2.35mmol) in dry diethylether (10ml) was treated with phosphorus pentachloride (0.52g, 2.5mmol) at room temperature for 2h. The mixture was concentrated and treated several times with toluene and again evaporated to dryness. The resulting acid chloride was dissolved in dry THF (5ml) and CH<sub>2</sub>Cl<sub>2</sub> (5ml) and cooled to 0 °C. *t*-Butyl-1-(benzyloxycarbonyl)-hexahydro-3-pyridazine-carboxylate (0.753g, 2.35mmol, 1 equiv) and *N*-ethylmorpholine (3ml) were added to the solution. The reaction mixture was stirred for 30min at 0 °C and then overnight at room temperature. The mixture was evaporated and the resulting residue taken up with CH<sub>2</sub>Cl<sub>2</sub> (30ml). The solution was washed with 1M HCl, water, 10% NaHCO<sub>3</sub>, dried (MgSO<sub>4</sub>) and evaporated. The resulting white foam was purified on silica gel (0-2% methanol in CH<sub>2</sub>Cl<sub>2</sub>) which afforded the required compound 251 as a pale yellow glassy solid (740mg, 39%):  $[\alpha]_D^{20}$  -22 (c 0.42, MeOH); IR (KBr) 3441, 2966, 1725, 1693, 1386, 1255, 1221, 1186, 1154, 1123, 1063, 724; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.94-7.89 (4H, m), 7.56-7.28 (5H, m), 6.84 (2H, 2s), 5.29-5.20 (2H, AB), 4.91-4.81 (1H, m), 4.05-3.88 (1H, m), 3.78 (3H, s), 3.75-3.80 (1H, m), 3.28-2.95 (2H, m), 2.23-1.51 (6H, m), 1.45 (9H, s), 1.31 (9H, s), 1.28 (9H, s), 1.27 (3H, d).

(1*S*, 8*S*, 9*S*) *t*-Butyl 6,10-dioxo-8-methyl-1,2,3,4,7,8,9,10-octahydro-9-phthalimido-6H-pyridazino[1,2-*a*][1,2]diazepin-1-carboxylate (254). A solution of the protected acid (251) (715mg, 0.893mmol)

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- in acetonitrile was treated with Cerium (IV) ammonium nitrate (1.8g, 3.3mmol, 3.7 equiv) in water (3ml) for 4h at room temperature. Mannitol (600mg, 3.3mmol, 3.7 equiv) was added and the mixture was stirred for 1h.
- 5 Diethylether (50ml) and water (30ml) were added to the mixture. After decantation, the aq. phase was extracted with diethylether (4 x 50ml). The combined organic phase was washed with water, dried ( $\text{MgSO}_4$ ) and concentrated. Chromatography on silica gel (10% methanol in  $\text{CH}_2\text{Cl}_2$ ) afforded 5-(1-benzoyloxycarbonyl-3-t-butoxycarbonyl-hexahydropyridazin-2-yl)carbonyl-3-methyl-4-phthalimidopentanoic acid (**252**) (360mg, 64%):  $[\alpha]_D^{20}$  -49.2 (c 0.118, MeOH). This product was used without further purification (360mg, 0.609mmol), and
- 15 was hydrogenated in methanol (30ml) using 10% Pd/carbon (36mg) for 3h. The reaction mixture was filtered and the resulting solution concentrated to afford the amine (**253**) as a foam (270mg, 96%)  $[\alpha]_D^{20}$  -56.1 (c 0.18 MeOH). The amine (**253**) was dissolved in dry THF (10ml) and
- 20 phosphorous pentachloride (305mg, 1.47mmol, 2.5 equiv) was added. The mixture was then cooled to -5 °C and N-ethylmorpholine was added under nitrogen. The reaction mixture was stirred overnight at room temperature. The mixture was concentrated and the residue taken up with
- 25  $\text{CH}_2\text{Cl}_2$  (20ml), cold  $\text{H}_2\text{O}$  (20ml), 1M HCl (20ml). After decantation, the aq. phase was reextracted with  $\text{CH}_2\text{Cl}_2$  (2 x 20ml). The combined organic phase was washed with 10%  $\text{NaHCO}_3$  and water, dried ( $\text{MgSO}_4$ ) and concentrated. The resulting oil was purified on silica gel (1% methanol in  $\text{CH}_2\text{Cl}_2$ ) affording the bicyclic compound
- 30 (**254**) as a solid (65mg, 25%):  $[\alpha]_D^{20}$  -77 (c 0.209, MeOH); IR (KBr) 3471, 3434, 2975, 2928, 1767, 1723, 1443, 1389, 1284, 1243, 1151, 1112, 720;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )

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$\delta$  7.94-7.69 (4H, m), 5.34-5.27 (1H, m), 4.89-4.66 (2H, m), 3.94-3.64 (2H, m), 3.02-2.84 (1H, m), 2.34-2.19 (2H, m), 1.94-1.61 (3H, m), 1.47 (9H, s), 1.14 (3H, d); Anal. Calcd for  $C_{23}H_{27}N_3O_6$ : C, 62.57; H, 6.17; N, 9.52.  
5 Found: C, 62.60; H, 6.40; N, 9.10.

(1S, 8S, 9S) t-Butyl-9-benzoylamino-6,10-dioxo-8-methyl-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxylate (255). A solution of the bicyclic compound (254) (70mg, 0.16mmol) in  
10 ethanol was treated with hydrazine hydrate (0.02ml, 4mmol, 2.5 equiv). After 5h stirring at room temperature, the mixture was concentrated and the resulting residue taken up in toluene and reevaporated. The residue was treated with 2M acetic acid (2ml) for  
15 16h. The resulting precipitate was filtered and washed with 2M acetic acid (10ml). The filtrate was basified with solid  $NaHCO_3$  and then extracted with EtOAc. The organic solution was washed with water, dried ( $MgSO_4$ ) and concentrated. Purification by flash chromatography  
20 on silica gel (2% methanol in  $CH_2Cl_2$ ) afforded the free amine as a foam (50mg, 100%). The amine (50mg, 0.16mmol) was dissolved in dioxane (1ml) and water (0.25ml) and treated with  $NaHCO_3$  (0.034g, 0.04mmol) followed by benzoylchloride (0.047ml, 0.40mmol, 2.8  
25 equiv). The mixture was stirred overnight at room temperature, then diluted with EtOAc (15ml). The organic solution was washed with 10%  $NaHCO_3$  and sat. aq.  $NaCl$ , dried ( $MgSO_4$ ) and concentrated. Purification by flash chromatography on silica gel (2% methanol in  
30  $CH_2Cl_2$ ) afforded the benzamide 255 as a foam (60mg, 100%):  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.89-7.39 (5H, m), 6.79 (1H, d), 5.32-5.20 (1H, m), 4.98-4.82 (1H, m), 4.75-4.64

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(1H, m), 3.84-3.65 (1H, m), 3.09-2.89 (1H, m), 2.45-2.16 (2H, m), 2.00-1.61 (4H, m), 1.48 (9H, s), 1.28 (3H, d).

- [3*S*(1*S*, 8*S*, 9*S*)] 3-(9-benzoylamino-6,10-dioxo-8-methyl-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-*a*][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (257). A solution of t-butyl ester 255 (67mg, 0.16mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1ml) was treated at 0 °C with trifluoroacetic acid (1ml). The resulting solution was stirred at 0 °C for 15min and then at room temperature for 1h. The solution was concentrated, the residue taken up in dry CH<sub>2</sub>Cl<sub>2</sub> (2 x 2ml) and the mixture again concentrated (x2). The residue was crystallized from diethylether. Filtration of the precipitate afforded the free acid of 255 as a grey solid (40mg, 70%). A solution of acid (40mg, 0.11mmol), N-allyloxycarbonyl-4-amino-5-benzyloxy-2-oxotetrahydrofuran (Chapman, Bioorg. & Med. Chem. Lett., 2, pp. 615-18 (1992); 39mg, 0.13mmol, 1.2equiv) and (Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub> (3mg) in a mixture of dry CH<sub>2</sub>Cl<sub>2</sub> (1ml) and dry DMF (0.2ml) was treated dropwise with n-Bu<sub>3</sub>SnH (0.089ml, 0.33mmol, 3 equiv). The resulting solution was stirred at 25 °C for 10min and then 1-hydroxybenzotriazole (36mg, 0.266mmol, 2.4 equiv) was added. The mixture was cooled to 0 °C and ethyldimethylaminopropyl carbodiimide (31mg, 0.16mmol, 1.5equiv) was added. After stirring at 0 °C for 10min and then at room temperature overnight, the mixture was diluted with EtOAc (20ml) and the resulting solution washed successively with 1M HCl (2 x 5ml), 10% NaHCO<sub>3</sub> (2 x 5ml) and sat. aq. NaCl (5ml), dried (MgSO<sub>4</sub>) and concentrated. Flash chromatography on silica gel (2 methanol in CH<sub>2</sub>Cl<sub>2</sub>) afforded a mixture of



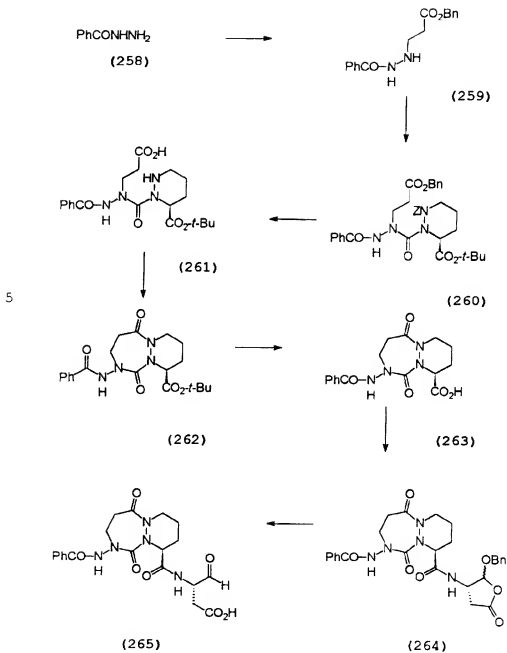
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diastereoisomers (256) as a grey solid (50mg, 82%).

This product (256) was used without further purification (50mg, 0.091mmol) and was hydrogenated in methanol (5ml) using 10% Pd/carbon (30mg) for 24h. The

5 reaction mixture was filtered and the resulting solution concentrated. Flash chromatography on silica gel (2-20% methanol in CH<sub>2</sub>Cl<sub>2</sub>) afforded compound 257 (9mg, 21%) as a white solid: <sup>1</sup>H NMR (D<sup>4</sup>-MeOH) δ 7.88-7.29 (5H, m), 5.18-4.99 (1H, m), 4.59-4.35 (3H, m),  
10 4.26-4.11 (1H, m), 3.65-3.41 (2H, m), 3.18-2.91 (1H, m), 2.62-1.47 (8H, m), 1.29-1.00 (3H, 2d) (mixture of acetal and hemiacetal). MS (ES -) 457.

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Benzyl 3-(N'-benzoylhydrazino)propanoate (259).

Benzyacrylate (1.13ml, 7.34mmol) was added to a stirred suspension of benzoylhydrazine (285) (1.0g, 7.34mmol) in isopropanol (20ml). The mixture was

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refluxed for 20h, cooled to room temperature then concentrated. The residue was purified by flash chromatography (20% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>) to afford **259** (1.098g, 50%) as an oil which crystallized on standing:  
5 mp 65 °C; IR (KBr) 3283, 1723, 1644, 1316, 1201, 1156;  
1H NMR (CDCl<sub>3</sub>) δ 8.32-8.18 (1H, m), 7.81-7.70 (2H, m),  
7.57-7.23 (8H, m), 5.36-4.92 (1H, brm), 5.11 (2H, s),  
3.26 (2H, t, J = 6.5), 2.59 (2H, t, J = 6.5); 13C NMR  
(CDCl<sub>3</sub>) δ 172.12, 167.27, 135.65, 132.54, 131.66,  
10 128.45, 128.10, 128.06, 126.84, 66.31, 47.33, 33.31;  
Anal. Calcd for C<sub>17</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>: C, 68.44; H, 6.08; N, 9.39.  
Found: C, 68.42; H, 6.10; N, 9.38. MS (ES +) 321 (M +  
Na, 38%), 299 (M<sup>+</sup> + 1, 100).

- (3S)-1-Benzyl 3-t-butyl 2-(N'-benzoyl-N-(2-  
15 benzyloxycarbonylethyl)hydrazinocarbonyl)hexahydro-  
pyridazine-1,3-dicarboxylate (**260**). A solution of  
(3S)-1-benzyl 3-t-butyl hexahydropyridazine-1,3-  
dicarboxylate (Hassall et al. J. Chem. Soc. Perkin 1,  
pp. 1451-1454 (1979)) (925.3mg, 2.89mmol) and  
20 diisopropylethylamine (0.70ml, 4.0mmol) in a 1.93M  
toluene solution of phosgene (17.96ml, 34.7mmol) was  
stirred at room temperature for 45min, then  
concentrated to leave a yellow solid. To this solid  
was added toluene (18ml), hydrazide (**259**) (861.6mg,  
25 2.89mmol) and diisopropylethylamine (0.70ml, 4.0mmol).  
The mixture was stirred at room temperature for 2.75h,  
then concentrated. The resulting residue was taken up  
in EtOAc, washed twice with 1M HCl, brine, then dried  
(MgSO<sub>4</sub>), filtered and concentrated to afford 2.15g of  
30 crude material. Flash chromatography (40% EtOAc in  
hexane) afforded 1.65g (89%) of the title compound as a  
white foam: mp 40 °C; [α]<sub>D</sub><sup>24</sup> -55.78 ° (c 0.40, CH<sub>2</sub>Cl<sub>2</sub>);

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IR (KBr) 3436, 2930, 1733, 1689, 1455, 1412', 1367, 1258, 1156, 697;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.54-8.23 (0.5H, m), 7.97-7.09 (15.5H), 5.16-4.80 (4H, m), 4.66-4.32 (1H, m), 4.24-3.55 (3.3H, m), 3.50-3.26 (0.4H, m), 3.19-2.49 (2.3H, m), 2.11-1.43 (6H, m), 1.32-1.05 (7H, m); Anal. Calcd for  $\text{C}_{35}\text{H}_{40}\text{N}_4\text{O}_8 \cdot 0.5\text{H}_2\text{O}$ : C, 64.31; H, 6.32; N, 8.57. Found: C, 64.18; H, 6.27; N, 8.56. MS (ES +) 662 ( $\text{M} + \text{Na}$ , 84%), 645 ( $\text{M}^+ + 1$ , 100), 384 (77).

(6S)-3-(N'-benzoyl-N-(6-t-butoxycarbonylhexa-  
 10 hydropyridazine-1-carbonyl)hydrazino)propanoic acid  
 (261). A solution of 260 (1.59g, 2.47mmol) in MeOH (142ml) was treated with 10% Palladium on carbon (230.0mg) and stirred under an atmosphere of  $\text{H}_2$  for 1.5h. The mixture was filtered and the solvent  
 15 evaporated to afford 1.04g (100%) of a white foam. This was used in the next step without further purification: mp <40 °C;  $[\alpha]_{\text{D}}^{26} +1.6^\circ$  (c 0.26,  $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3422, 2977, 2986, 1728, 1677, 1486, 1445, 1396, 1369, 1309, 1228, 1155, 916, 716;  $^1\text{H}$  NMR  
 20 ( $\text{CDCl}_3$ )  $\delta$  10.0-9.7 (1H, brm), 7.86 (2H, d,  $J = 7.5$ ), 7.62-7.38 (3H, m), 7.3-5.6 (2H, brm), 4.57 (1H, brd,  $J = 4.0$ ), 4.05-3.77 (2H, m), 3.00-2.82 (1H, m), 2.80-2.43 (3H, m), 2.20-2.03 (1H, m), 2.00-1.47 (1H, m), 1.62-1.14 (11H, m);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  175.00, 171.17, 167.62,  
 25 160.68, 132.39, 131.77, 128.67, 127.38, 82.27, 54.38, 48.04, 46.35, 33.62, 28.02, 25.68, 21.61. MS (ES -) 443 ( $\text{M} + \text{Na}$ , 68%), 421 ( $\text{M}^+ + 1$ , 100), 365 (50), 131 (61).

(4S) t-Butyl 7-benzamido-6,10-dioxo-1,2,3,4,7,8,9,10-  
 30 octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-  
 carboxylate (262). To a solution of amino acid 261

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(1.012g, 2.41mmol) in dry THF (26ml) at 0 °C was added N-ethylmorpholine (597µl, 4.69mmol), followed by  $\text{PCl}_5$  (651.3mg, 3.12mmol). The reaction was stirred at 0 °C for 2h, then allowed to warm to rt and stirred for a further 15.5h. The mixture was concentrated and the resulting residue taken up in EtOAc, washed twice with 1M HCl, sat.  $\text{NaHCO}_3$ , brine, then dried ( $\text{MgSO}_4$ ), filtered and concentrated. Flash chromatography (20% EtOAc in  $\text{CH}_2\text{Cl}_2$ ) gave 727.3mg (75%) of the title compound as a white foam:  $[\alpha]_D^{26} +51.0^\circ$  (c 0.20,  $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3436, 2979, 1733, 1670, 1483, 1437, 1420, 1299, 1243, 1156;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.70 (1H, s), 7.78 (2H, d,  $J = 7.0$ ), 7.57-7.32 (3H, m), 5.08 (1H, dd,  $J = 2.5, 5.5$ ), 4.59-4.43 (1H, m), 4.08-3.69 (3H, m), 3.07-2.84 (1H, m), 2.57-2.35 (1H, m), 2.34-2.14 (1H, m), 2.07-1.43 (3H, m), 1.48 (9H, s);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  172.41, 169.04, 166.35, 158.35, 132.24, 132.03, 128.61, 127.31, 82.77, 55.41, 54.07, 41.57, 32.21, 28.04, 24.97, 20.37; Anal. Calcd for  $\text{C}_{20}\text{H}_{26}\text{N}_4\text{O}_5$ : C, 59.69; H, 6.51; N, 13.92. Found: C, 59.53; H, 6.53; N, 13.84. MS (ES +) 425 ( $\text{M} + \text{Na}$ , 71%), 403 ( $\text{M}^+ + 1$ , 100), 145 (41).

**(4S)-7-Benzamido-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic Acid (263).** A solution of ester **262** (720.0mg, 1.80mmol) in a 1:1 mixture of  $\text{CH}_2\text{Cl}_2$  and TFA (150ml) was stirred for 1.3h under a dry atmosphere. The solution was then reduced in vacuo, taken up in  $\text{Et}_2\text{O}$  and reduced again. This process was repeated six times to afford the crude product as an off-white solid. The product was purified by flash chromatography (5% MeOH in  $\text{CH}_2\text{Cl}_2$ ) to afford 520.0mg (83%) of the title compound as a white

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foam:  $[\alpha]_D^{25} +59.5^\circ$  (c 1.82,  $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3435, 3266, 2956, 1732, 1664, 1524, 1486, 1440, 1302;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  9.13 (1H, s), 7.77 (2H, d,  $J = 7.5$ ), 7.57-7.32 (3H, m), 5.27-5.16 (1H, m), 4.62-4.43 (1H, m), 4.09-2.70 (3H, m), 3.14-2.89 (1H, m), 2.59-2.43 (1H, m), 2.38-2.20 (1H, m), 2.14-1.89 (1H, m), 1.82-1.59 (2H, m);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  173.65, 172.28, 166.44, 158.42, 132.44, 131.31, 128.61, 127.39, 54.83, 54.01, 42.11, 31.79, 24.42, 20.29; MS (ES  $-$ ) 345 (M -  $\text{H}^+$ , 100%), 161 (45).

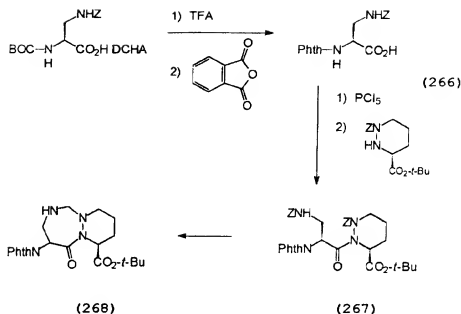
[2*RS*,3*S*(4*S*)] N-(2-Benzylloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide (264). To a solution of acid 263 (300.0mg, 0.87mmol) and (2*RS*,3*S*)-3-allyloxycarbonylamino-2-benzylloxy-5-oxotetrahydrofuran (Chapman, Bioorg. & Med. Chem. Lett. 2, pp. 615-18 (1992)) (277.6mg, 0.95mmol) in dry  $\text{CH}_2\text{Cl}_2$  (2.5ml) and dry DMF (2.5ml) at rt was added bis(triphenylphosphine) palladium chloride (13.0mg), followed by tri-*n*-butyltin hydride (466.0 $\mu$ l, 1.73mmol). The reaction was stirred for 5min, then 1-hydroxybenzotriazole (234.1mg, 1.73mmol) was added and the mixture was cooled to 0  $^\circ\text{C}$  before addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (204.5mg, 1.04mmol). The mixture was allowed to warm to rt and stirred for 16.5h. The mixture was diluted with EtOAc, washed with 1M  $\text{NaHSO}_4$  twice with sat.  $\text{NaHCO}_3$ , then  $\text{H}_2\text{O}$  and brine. The organic layer was dried ( $\text{MgSO}_4$ ), filtered and concentrated. The residue was purified by flash chromatography (5% MeOH in  $\text{CH}_2\text{Cl}_2$ ) to afford 358.3mg (77%) of the title compound as a white solid: IR (KBr) 3435, 1791, 1665, 1526,

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1421, 1285;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.76 and 8.49 (1H, 2 x s), 7.92-7.73 (2H, m), 7.62-7.24 (8.5H, m), 6.86 (0.5H, d,  $J = 8.0$ ), 5.53 and 5.33 (1H, d,  $J = 5.5$ , s), 4.95-4.34 (5H, m), 4.04-3.54 (3H, m), 3.03-2.64 (2H, m), 2.49-2.14 (2H, m), 2.11-1.46 (4H, m); MS (ES +) 558 (M + Na, 100%), 536 ( $\text{M}^+ + 1$ , 78), 404 (58).

[3S(4S)]3-(7-Benzamido-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido)-4-oxobutanoic acid (265). A mixture of  
10 264 (350.0mg, 0.65mmol), 10% palladium on carbon (350mg) and methanol (36mL) was stirred under an atmosphere of  $\text{H}_2$  for 6.5h. The mixture was filtered and the solvent evaporated.  $\text{Et}_2\text{O}$  was added and the solvent removed again. This process was repeated four  
15 times to reveal 283mg (97%) of the title compound, as a white crystalline solid: mp decarboxylates above 140 °C;  $[\alpha]_{\text{D}}^{26} +33.5^\circ$  (c 0.18, MeOH), IR (KBr) 3428, 1663, 1528, 1487, 1437, 1288;  $^1\text{H}$  NMR ( $\text{D}_6\text{-DMSO}$ )  $\delta$  10.56 (1H, s), 8.71-8.57 (1H, m), 7.88-7.81 (2H, m), 7.65-7.46 (3H, m), 4.97-4.85 (1H, m), 4.38-4.0 (3H, m),  
20 3.88-3.52 (3H, m), 2.91-2.71 (2H, m), 2.50-2.36 (1H, m), 2.35-2.21 (1H, m), 2.10-1.94 (1H, m), 1.93-1.49 (3H, m);  $^{13}\text{C}$  NMR ( $\text{D}_6\text{-DMSO}$ )  $\delta$  173.66, 172.49, 169.97, 169.89, 164.96, 157.62, 132.35, 131.85, 128.39, 127.32,  
25 53.81, 52.69, 40.90, 33.17, 31.60, 24.40, 24.13, 19.24; MS (ES -).

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**(2S) 3-Benzoyloxycarbonylamino-2-phthalimidopropionic**

**acid (266).** A solution of (2S)-3-

benzyloxycarbonylamino-2-tert-

butoxycarbonylamino-2-phthalimidopropionic

salt (3g, 5.8mmol) in dichloromethane (200ml) was washed four times with 1M HCl solution, dried (MgSO<sub>4</sub>)

and concentrated. The resulting oil was dissolved in dry dichloromethane (35ml), cooled to 0 °C and treated

with trifluoroacetic acid (35ml). This solution was stirred at 0 °C for 1.5h then evaporated to dryness.

Dichloromethane (50ml) was added to the residue then removed under vacuum. This process repeated six times

to afford a white solid. The white solid was suspended in toluene (50ml), treated with powdered phthalic

anhydride (940mg, 6.35mmol) and refluxed for 18h. The resulting solution was concentrated to afford an oil

which was purified by flash chromatography (2-10% methanol/dichloromethane) to afford **266**, 2.01g (94%) as a white powder: IR (KBr) 3600-2500br, 1776, 1714,



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1530, 1469, 1455, 1392, 1263, 1131, 722;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.83 (2H, m), 7.72 (2H, m), 7.29 (5H, m), 5.41 (1H, m), 5.03 (2H, s), 3.90 (2H, m); MS (ES-), 367 (M - 1).

[3S (2S)] t-Butyl 1-benzyloxycarbonyl-2-(3-

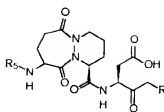
- 5 benzyloxycarbonylamino-2-phthalimidopropionyl)pyridazine-3-carboxylate (267). A suspension of the acid 266 (1.32g, 3.58mmol) in dry ether (37ml) was treated with phosphorus pentachloride (1.04g, 5mmol) and stirred at room temperature for 2h.
- 10 The solution was filtered to remove unreacted phosphorus pentachloride then evaporated to dryness. The residue was treated with dry toluene (25ml) then evaporated to dryness. This process was repeated several times. The resulting oil was dissolved in dry
- 15 dichloromethane (25ml), cooled to 0 °C and treated with a solution of (3S) t-butyl 1-benzyloxycarbonylpyridazine-3-carboxylate (1.15g, 3.58mmol) in dry dichloromethane (2ml) followed by 5% aqueous sodium bicarbonate solution (25ml). The
- 20 mixture was stirred rapidly at room temperature for 20h then diluted with ethyl acetate (100ml) and acidified to pH2 with 1M HCl. The organic phase was washed twice with dilute HCl solution then brine, dried ( $\text{MgSO}_4$ ) and concentrated. The resulting oil was purified by flash
- 25 chromatography (2-20% ethyl acetate/dichloromethane then 10-20% methanol/dichloromethane) to afford (267), 1.25g (52%) as a white powder: IR (KBr) 3367, 2955, 1722, 1517, 1455, 1387, 1369, 1251, 1153, 721;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.81 (2H, m), 7.74 (2H, m), 7.63 (1H, brs),
- 30 7.31 (10H, m), 5.46-4.76 (5H, m), 4.07-3.54 (4H, m), 2.4 (1H, m), 2.0-1.6 (3H, m), 1.40 (9H, s); MS (ES+), 671 (M + 1), 693 (M + Na).

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(1*S*,9*S*) *t*-Butyl 1,2,3,4,7,8,9,10-octahydro-10-oxo-9-phthalimido-6H-pyridazino[1,2-*a*][1,2,4]triazepine-1-carboxylate (**268**). A solution of ester **267** (50mg, 0.074mmol) in methanol (15ml) was treated with 10% palladium on carbon (50mg) and hydrogenated at room temperature and atmospheric pressure for 24h. The mixture was evacuated thoroughly to remove hydrogen then treated with 37% aqueous formaldehyde (18mg, 0.22mmol) and stirred under nitrogen for 2h. The mixture was filtered, evaporated to dryness and the product purified by flash chromatography (4-100% ethyl acetate/dichloromethane) to afford **268** 14.5mg (48%) as an oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.85 (2H, m), 7.71 (2H, m), 5.78 (1H, dd, *J* = 10, 5), 4.99 (1H, dd, *J* = 6.1, 1.5), 4.07 (1H, d, *J* = 10.6), 3.49 (1H, dd, *J* = 14, 5), 3.39 (1H, d, *J* = 10.3), 3.24 (1H, dd, *J* = 14, 10.2), 3.17 (2H, m), 2.39 (1H, m), 1.84-1.46 (3H), 1.51 (9H, s); MS (ES<sup>+</sup>), 415 (*M* + 1), 437 (*M* + Na).

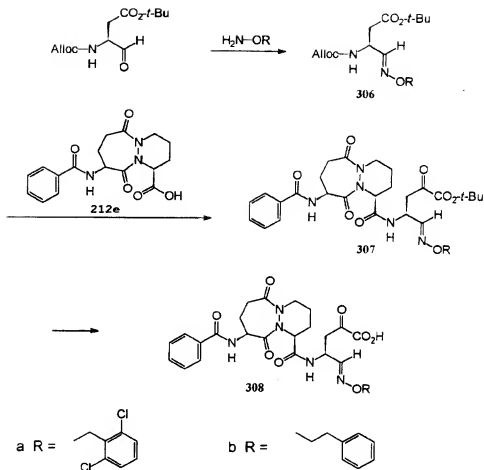
Compounds **280-283** were prepared from **212b** by a method similar to the method used to prepare **226e**. Compounds **284-287** were prepared by a method similar to the method used to prepare **217e**.

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**280-287**

| compound | R <sub>5</sub> | R |
|----------|----------------|---|
| 280      |                |   |
| 281      |                |   |
| 282      |                |   |
| 283      |                |   |
| 284      |                |   |
| 285      |                |   |
| 286      |                |   |
| 287      |                |   |

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(3*S*) 3-Allyloxycarbonylamino-4-oxobutyric acid tert-butyl ester O-(2,6-dichlorophenylmethyl)oxime (306a) was prepared by a similar procedure as 208a except that 2,6-dichlorophenylmethoxyamine (prepared by a similar method as 306b) was used instead of semicarbazide to give 870mg (quant.) as a clear oil.

(3*S*) 3-Allyloxycarbonylamino-4-oxobutyric acid tert-butyl ester O-(2-(phenyl)ethyl)oxime (306b) was prepared by a similar procedure as 208a except that 2-

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(phenyl)ethoxyamine (US 5 346 911) was used instead of semicarbazide to give 395mg (quant.) as a clear oil.

[3*S*(1*S*,9*S*) 3-(9-Benzoylamino-6,10-dioxo-

1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-

5 [1,2-*a*][1,2]diazapine-1-carboxamido)-amino]-4-

oxobutanoic acid *t*-butyl ester, O-(2,6-

dichlorophenylmethyl)oxime (307a) was prepared by a

procedure similar to 233e except 306a was used instead

of 207a to give 23 mg(23%) of 307a as a white solid.

10 [3*S*(1*S*,9*S*) 3-(9-Benzoylamino-6,10-dioxo-

1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-

[1,2-*a*][1,2]diazapine-1-carboxamido)-amino]-4-

oxobutanoic acid *t*-butyl ester, O-(2-

(phenyl)ethyl)oxime (307b) was prepared by a procedure

15 similar to 233e except 306b was used instead of 207a to give 43 mg(48%) of 307b as a white solid.

[3*S*(1*S*,9*S*) 3-(9-Benzoylamino-6,10-dioxo-

1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-

[1,2-*a*][1,2]diazapine-1-carboxamido)-amino]-4-

20 oxobutanoic acid, O-(2,6-dichlorophenylmethyl)oxime

(308a) was prepared by from 307a a procedure similar to

the preparation of 235e from 234e to give 15.2 mg (74%)

as white solid: <sup>1</sup>H NMR(CD<sub>3</sub>OD) δ 0.9(m), 1.3(s),

1.7(m), 1.8(m), 2.0(m), 2.1-2.2(m), 2.3(dd), 2.4-

25 2.5(m), 2.6(m), 2.7-2.8(m), 3.1(m), 3.3(m), 3.4-3.5(m),

4.5(m), 4.9(m), 5.1(m), 5.3(d), 5.4(s), 6.8(d), 7.2-

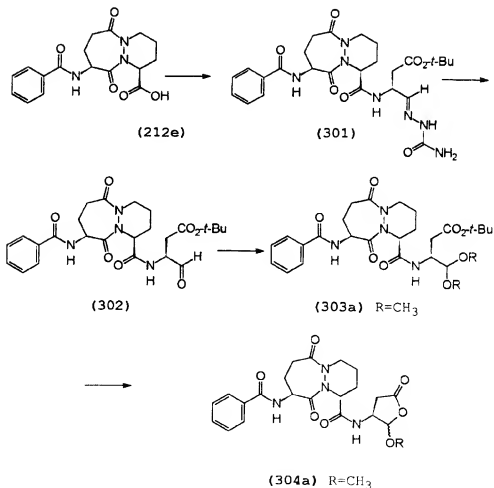
7.5(m), 7.8(dd), 8.4(dd).

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[3*S*(1*S*,9*S*) 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino-[1,2-*a*][1,2]diazapine-1-carboxamido)-amino]-4-oxobutanoic acid, *O*-(2-(phenyl)ethyl)oxime (308b) was

5 prepared by from 307b a procedure similar to the preparation of 235e from 234a to give 25.2 mg (68%) as white solid:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  1.2(m), 1.6-1.7(m), 2.0-2.1(m), 2.2(m), 2.3(m), 2.5(m), 2.6-2.7(dd), 2.9(t), 3.0(t), 3.1(m), 3.3-3.5(m), 4.2(t), 4.25(m), 4.5(m),

10 5.2(t), 5.3(t), 6.7(d), 7.1-7.2(m), 7.35(dd), 7.4(m), 7.5(m), 7.8(dd), 8.3(dd).



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[3*S*(1*S*,9*S*) 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6*H*-pyriazino-[1,2-*a*][1,2]diazapine-1-carboxamido)-amino]-4-oxobutanoic acid *tert*-butyl ester (302).

- 5 **Step A:** 301 was prepared by procedure similar to 605a (Step A), except 212e was used instead of 603a to give 540 mg (34%) to give a white solid.

- Step B:** 302. A solution of 301 (50.7 mg; 0.091 mmol) in 2.8 ml of MeOH/HOAc/37% aq. formaldehyde (5:1:1) was  
10 stirred at rt for 5.5 h. and the reaction was concentrated to 0.7 ml *in vacuo*. The residue was dissolved in 3 ml of CH<sub>3</sub>CN and concentrated to 0.7 ml (3x), dissolved in toluene and concentrated to 0.7 ml *in vacuo* (2x), and concentrated to dryness.  
15 Chromatography (flash, SiO<sub>2</sub>, 5% isopropanol/CH<sub>2</sub>Cl<sub>2</sub>) gave 302 (45.5 mg, 78%) as a white solid: <sup>1</sup>H NMR(DMSO-*d*<sub>6</sub>) δ 1.0-1.15(m, 2H), 1.4(s, 9H), 1.65(m, 2H), 1.9-2.1(m, 2H), 2.15-2.4(m, 3H), 2.55(m, 1H), 2.7-3.0(m, 2H), 4.3-4.6(m, 2H), 4.9(m, 1H), 5.2(m, 1H), 7.4-7.6(m, 2H),  
20 7.8-8.0(m, 2H), 8.6(m, 1H), 8.8(m, 1H), 9.4(s, 1H).

[1*S*,9*S* (2*RS*,3*S*)] 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-*N*-(2-methoxy-5-oxo-tetrahydro-furan-3-yl)-6*H*-pyridazino[1,2-*a*][1,2]diazapine-1-carboxamide. (304a).

- 25 **Step A:** A solution of 302 (90 mg; 0.18 mmol) in 10 ml of MeOH was treated with trimethylorthoformate (1ml) and *p*-toluene sulfonic acid hydrate (5 mg; 0.026 mmol) and the reaction was stirred for 20 h. The reaction was treated with 3 ml of aq. sat. NaHCO<sub>3</sub> and  
30 concentrated *in vacuo*. The residue was taken up in

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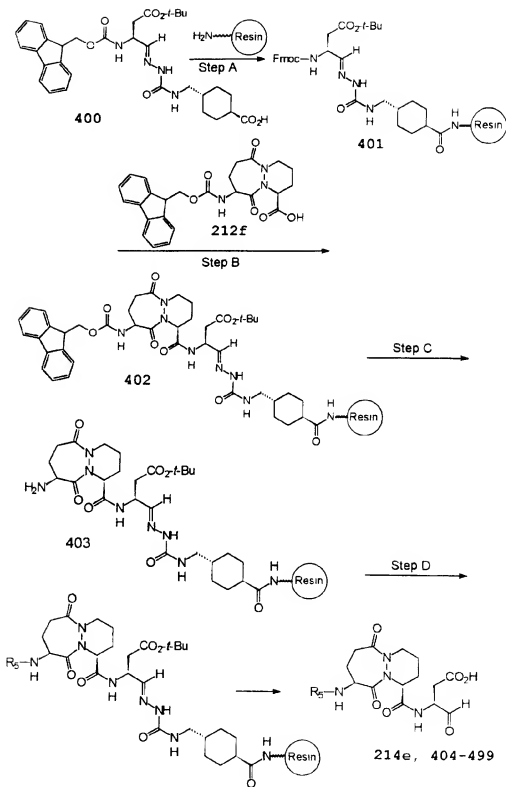
EtOAc and washed with dilute aq.  $\text{NaHCO}_3$ , dried over  $\text{MgSO}_4$  and concentrated *in vacuo* to give 80 mg of **303a**.  
**Step B:** **303a** was dissolved in 2 ml of TFA and stirred at rt for 15 min. The reaction was dissolved in  $\text{CH}_2\text{Cl}_2$  and concentrated *in vacuo* (3x). Chromatography (flash,  $\text{SiO}_2$ , 1% to 3%  $\text{MeOH}/\text{CH}_2\text{Cl}_2$  gave 43 mg (64%) of **304a** as a white solid:  $^1\text{H}$  NMR( $\text{CDCl}_3$ )  $\delta$  1.55-1.8(m, 2H), 1.9-2.15(m, 4H), 2.25-2.5(m, 2H), 2.7-3.3(m, 4H), 3.45, 3.6(s, s, 3H), 4.4, 4.75(2m, 1H), 4.6(m, 1H), 4.95, 5.4(t,d, 1H), 5.1-5.2(m, 1H), 6.45, 7.05(2d, 1H), 6.95(m, 1H), 7.45(m, 2H), 7.5(m, 1H), 7.85(m, 2H).

#### Example 11

Compounds **214e**, **404-413**, **415-445**, **446-468**, **470-491**, and **493-499** were synthesized as described in Example 11 and Table 7.



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- Step A. Synthesis of 401.** TentaGel S<sup>®</sup> NH<sub>2</sub> resin (0.16 mmol/g, 10.0 g) was placed in a sintered glass funnel and washed with DMF (3 x 50 mL), 10% (v/v) DIEA in DMF (2 x 50 mL) and finally with DMF (4 x 50 mL).
- 5 Sufficient DMF was added to the resin to obtain a slurry followed by **400** (1.42 g, 2.4 mmol, prepared from (3S)-3-(fluorenylmethyloxycarbonyl)-4-oxobutyric acid t-butyl ester according to A.M. Murphy et. al. J. Am. Chem. Soc., 114, 3156-3157 (1992)), 1-
- 10 hydroxybenzotriazole hydrate (HOBt·H<sub>2</sub>O; 0.367 g, 2.4 mmol), *O*-benzotriazol-1-yl-*N,N,N'*-tetramethyluronium hexafluorophosphate (HBTU; 0.91 g, 2.4 mmol), and DIEA (0.55 mL, 3.2 mmol). The reaction mixture was agitated overnight at rt using a wrist arm shaker. The resin
- 15 was isolated on a sintered glass funnel by suction filtration and washed with DMF (3 x 50 mL). Unreacted amine groups were then capped by reacting the resin with 20% (v/v) Ac<sub>2</sub>O/DMF (2 x 25 mL) directly in the funnel (10 min/wash). The resin was washed with DMF (3
- 20 x 50 mL) and CH<sub>2</sub>Cl<sub>2</sub> (3 x 50 mL) prior to drying overnight in vacuo to yield **401** (11.0 g, quantitative yield).

- Step B. Synthesis of 402.** Resin **401** (6.0 g, 0.16 mmol/g, 0.96 mmol) was swelled in a sintered glass
- 25 funnel by washing with DMF (3 x 25 mL). The Fmoc protecting group was then cleaved with 25% (v/v) piperidine/DMF (25 mL) for 10 min (intermittent stirring) and then for 20 min with fresh piperidine reagent (25 mL). The resin was then washed with DMF (3
- 30 x 25 mL), followed by *N*-methypyrrolidone (2 x 25 mL). After transferring the resin to a 100 mL flask, *N*-methypyrrolidone was added to obtain a slurry followed

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by **212F** (0.725 g, 1.57 mmol), HOBT·H<sub>2</sub>O (0.25 g, 1.6 mmol), HBTU (0.61 g, 1.6 mmol) and DIEA (0.84 mL, 4.8 mmol). The reaction mixture was agitated overnight at rt using a wrist arm shaker. The resin work-up and  
5 capping with 20% (v/v) Ac<sub>2</sub>O in DMF were performed as described for **401** to yield **402** (6.21 g, quantitative yield).

**Step C. Synthesis of 403.** This compound was prepared from resin **402** (0.24 g, 0.038 mmol) using an  
10 Advanced ChemTech 396 Multiple Peptide synthesizer. The automated cycles consisted of a resin wash with DMF (3 x 1 mL), deprotection with 25% (v/v) piperidine in DMF (1 mL) for 3 min followed by fresh reagent (1 mL) for 10 min to yield resin **403**. The resin was washed  
15 with DMF (3 x 1 mL) and *N*-methypyrrolidone (3 x 1 mL).

**Step D. Method 1. [3S(1S,9S)]-3-(6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-9-(thiophene-3-carboxylamino)-6H-pyridazine[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (409).** Resin **403** was  
20 acylated with a solution of 0.4M thiophene-3-carboxylic acid and 0.4M HOBT in *N*-methypyrrolidone (1 mL), a solution of 0.4M HBTU in *N*-methypyrrolidone (0.5 mL) and a solution of 1.6M DIEA in *N*-methypyrrolidone (0.35 mL) and the reaction was shaken for 2 hr at rt. The  
25 acylation step was repeated. Finally, the resin was washed with DMF (3 x 1 mL), CH<sub>2</sub>Cl<sub>2</sub> (3 x 1 mL) and dried *in vacuo*. The aldehyde was cleaved from the resin and globally deprotected by treatment with 95% TFA/5% H<sub>2</sub>O (v/v, 1.5 mL for 30 min at rt. After washing the  
30 resin with cleavage reagent (1 mL), the combined filtrates were added to cold 1:1 Et<sub>2</sub>O:pentane (12 mL)

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and the resulting precipitate was isolated by centrifugation and decantation. The resulting pellet was dissolved in 10% CH<sub>3</sub>CN/90% H<sub>2</sub>O/0.1% TFA (15 mL) and lyophilized to obtain crude **409** as a white powder. The  
5 compound was purified by semi-prep RP-HPLC with a Rainin Microsorb™ C18 column (5  $\mu$ , 21.4 x 250 mm) eluting with a linear CH<sub>3</sub>CN gradient (5% - 45%) containing 0.1% TFA (v/v) over 45 min at 12 mL/min. Fractions containing the desired product were pooled  
10 and lyophilized to provide **409** (10.8 mg, 63%).

**Step D. Method 1A. Synthesis of 418.** Following a similar procedure as method 1, resin **403** was acylated with 4-(1-fluorenylmethoxycarbonylamino)benzoic acid and repeated. The Fmoc group was removed as described  
15 in Step C and the free amine was acetylated with 20% (v/v) Ac<sub>2</sub>O in DMF (1 mL) and 1.6M DIEA in *N*-methylpyrrolidone (0.35 mL) for 2 hr at rt. The acetylation step was repeated. Cleavage of the aldehyde from the resin gave **418** (3.2 mg).

20 **Step D. Method 1B. Synthesis of 447.** Following a similar procedure as method 1A, resin **403** was acylated with 0.4M 4-(1-fluorenylmethoxycarbonylamino)benzoic acid. The acylation step was repeated once. The Fmoc group was  
25 removed as before and the free amine was reacted with 1M methanesulfonyl chloride in CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL) and 1M pyridine in CH<sub>2</sub>Cl<sub>2</sub> (0.60 mL) for 4 hr at rt. Cleavage of the aldehyde from the resin gave **447** (10.0 mg).

**Step D. Method 2. Synthesis of 214e.** Following  
30 a similar procedure as method 1, resin **403** was acylated

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with 0.5M benzoyl chloride in *N*-methypyrrolidone (1 mL) and 1.6M DIEA in *N*-methypyrrolidone (0.35 mL) for 2 hr at rt. The acylation step was repeated. Cleavage of the aldehyde from the resin gave **214e** (5.1 mg, 30%).

- 5       **Step D. Method 3. Synthesis of 427.** Following a similar procedure as method 1, resin **403** was reacted with 1.0M benzenesulfonyl chloride in  $\text{CH}_2\text{Cl}_2$  (0.5 mL) and 1M pyridine in  $\text{CH}_2\text{Cl}_2$  (0.60 mL) for 4 hr at rt. The reaction was repeated. Cleavage of the aldehyde  
10 from the resin gave **427** (7.2 mg, 40%).

- Step D. Method 4. Synthesis of 420.** Following a similar procedure as method 1, resin **403** was reacted with 0.5M methylisocyanate in *N*-methypyrrolidone (1 mL) and 1.6M DIEA in *N*-methypyrrolidone (0.35 mL) for 2  
15 hr at rt. The reaction was repeated. Cleavage of the aldehyde from the resin gave **420** (8.3 mg, 55%).

- Step D. Method 5. Synthesis of 445.** Following a similar procedure at method 1, resin **403** was acylated with 0.27M imidazole-2-carboxylic acid (1 mL) in 2:1  
20 DMF:H<sub>2</sub>O (with 1 eq. DIEA) and 1M 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) in 2:1 *N*-methypyrrolidone/H<sub>2</sub>O (0.35 mL) for 3 hr at rt. Cleavage of the aldehyde from the resin gave **445** (9.5 mg).

- 25   **Analytical HPLC methods:**

(1) Waters DeltaPak C18, 300A (5 $\mu$ , 3.9 x 150 mm).  
Linear  $\text{CH}_3\text{CN}$  gradient (5% - 45%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.

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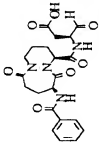
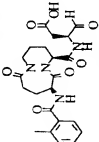
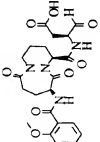
(2) Waters DeltaPak C18, 300A (5 $\mu$ , 3.9 x 150 mm).  
Linear CH<sub>3</sub>CN gradient (0% - 25%) containing 0.1% TFA  
(v/v) over 14 min at 1 mL/min.

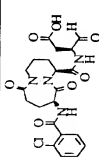
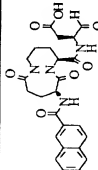
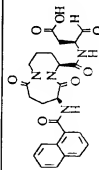
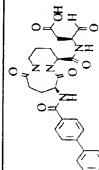
(3) Waters DeltaPak C18, 300A (5 $\mu$ , 3.9 x 150 mm).  
5 Isocratic elution with 0.1% TFA/water (v/v) at 1  
mL/min.

(4) Waters DeltaPak C18, 300A (5 $\mu$ , 3.9 x 150 mm).  
Linear CH<sub>3</sub>CN gradient (0% - 30%) containing 0.1% TFA  
(v/v) over 14 min at 1 mL/min.

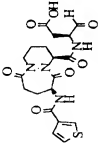
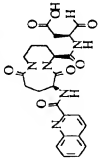
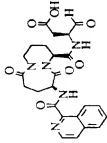
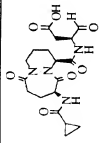
10 (5) Waters DeltaPak C18, 300A (5 $\mu$ , 3.9 x 150 mm).  
Linear CH<sub>3</sub>CN gradient (0% - 35%) containing 0.1% TFA  
(v/v) over 14 min at 1 mL/min.

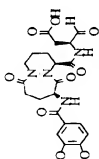
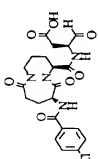
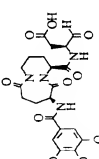
Table 7

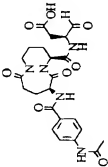
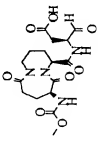
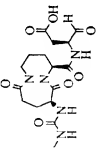
| Compd. | Structure  | MF  | MW     | HPLC RT<br>min  | MS<br>(M+H) <sup>+</sup> | Syn.<br>Method |
|--------|--|---|--------|-----------------|--------------------------|----------------|
| 214e   |  | C <sub>21</sub> H <sub>24</sub> N <sub>4</sub> O <sub>7</sub> | 444.45 | 6.67 (2)<br>98% | 445                      | 2              |
| 404    |  | C <sub>22</sub> H <sub>26</sub> N <sub>4</sub> O <sub>7</sub> | 458.48 | 6.66 (2)<br>97% | 459                      | 2              |
| 405    |  | C <sub>22</sub> H <sub>26</sub> N <sub>4</sub> O <sub>8</sub> | 474.47 | 8.2 (1)<br>98%  | 475                      | 2              |

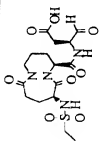
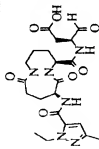
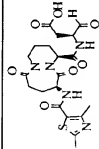
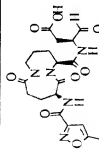
| Compd. | Structure  | MF  | MW     | HPLC RT<br>min   | MS<br>(M+H) <sup>+</sup> | Syn.<br>Method |
|--------|--|---|--------|------------------|--------------------------|----------------|
| 406    |  | C <sub>21</sub> H <sub>23</sub> ClN <sub>4</sub> O <sub>7</sub> | 478.89 | 6.33 (1)<br>98%  | 479                      | 2              |
| 407    |  | C <sub>25</sub> H <sub>26</sub> N <sub>4</sub> O <sub>7</sub>   | 494.51 | 9.90 (1)<br>98%  | 495                      | 2              |
| 408    |  | C <sub>25</sub> H <sub>26</sub> N <sub>4</sub> O <sub>7</sub>   | 494.51 | 9.0 (1)<br>98%   | 495                      | 2              |
| 409    |  | C <sub>27</sub> H <sub>28</sub> N <sub>4</sub> O <sub>7</sub>   | 520.55 | 11.14 (1)<br>98% | 521                      | 2              |

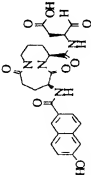
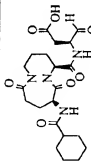
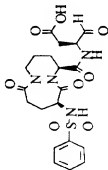


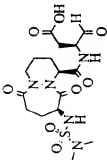
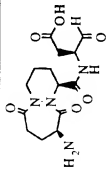
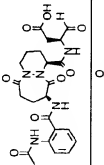
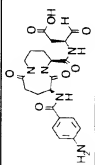
| Cmpd. | Structure  | MF          | MW     | HPLC RT<br>min  | MS<br>(M+H) <sup>+</sup> | Syn.<br>Method |
|-------|--|-------------|--------|-----------------|--------------------------|----------------|
| 410   |  | C19H22N4O7S | 450.47 | 4.87 (1)<br>98% | 451                      | 1              |
| 411   |  | C24H25N5O7  | 495.50 | 10.7 (1)<br>98% | 496                      | 1              |
| 412   |  | C24H25N5O7  | 495.50 | 8.57 (1)<br>98% | 496                      | 1              |
| 413   |  | C18H24N4O7  | 408.41 | 7.21 (2)<br>98% | 409                      | 1              |

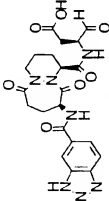
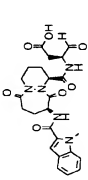
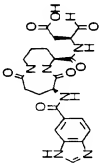
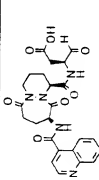
| Compd. | Structure  | MF  | MW     | HPLC RT<br>min  | MS<br>(M+H) <sup>+</sup> | Syn.<br>Method |
|--------|--|---|--------|-----------------|--------------------------|----------------|
| 415    |  | C <sub>22</sub> H <sub>24</sub> N <sub>4</sub> O <sub>9</sub>   | 488.46 | 7.58 (1)<br>98% | 489                      | 1              |
| 416    |  | C <sub>21</sub> H <sub>23</sub> ClN <sub>4</sub> O <sub>7</sub> | 478.89 | 9.66 (1)<br>98% | 479                      | 1              |
| 417    |  | C <sub>24</sub> H <sub>30</sub> N <sub>4</sub> O <sub>10</sub>  | 534.53 | 8.12 (1)<br>535 | 535                      | 1              |

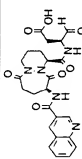
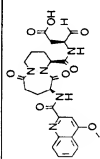
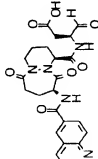
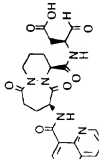
| Compd. | Structure  | MF  | MW     | HPLC RT<br>min  | MS<br>(M+H) <sup>+</sup> | Syn.<br>Method |
|--------|--|---|--------|-----------------|--------------------------|----------------|
| 418    |  | C <sub>23</sub> H <sub>27</sub> N <sub>5</sub> O <sub>8</sub> | 501.50 | 5.93 (1)<br>98% | 502                      | 1A             |
| 419    |  | C <sub>16</sub> H <sub>22</sub> N <sub>4</sub> O <sub>8</sub> | 398.38 | 6.84 (2)<br>98% | 399                      | 2              |
| 420    |  | C <sub>16</sub> H <sub>23</sub> N <sub>5</sub> O <sub>7</sub> | 397.39 | 5.25 (2)<br>98% | 398                      | 4              |

| Compd. | Structure  | MF          | MW     | HPLC RT<br>min              | MS<br>(M+H) <sup>+</sup> | Syn.<br>Method |
|--------|--|-------------|--------|-----------------------------|--------------------------|----------------|
| 421    |  | C16H24N4O8S | 432.46 | 7.13 (2)<br>98 <sub>3</sub> | 433                      | 3              |
| 422    |  | C21H26N6O7  | 476.49 | 6.89 (1)<br>98 <sub>3</sub> | 477                      | 1              |
| 423    |  | C20H25N5O7S | 479.52 | 5.62 (1)<br>98 <sub>3</sub> | 480                      | 1              |
| 424    |  | C19H23N5O8  | 449.42 | 6.28 (1)<br>450             | 450                      | 1              |

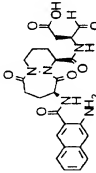
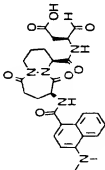
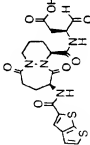
| Compd. | Structure  | ME          | MW     | HPLC RT<br>min  | MS<br>(M+H) + | Syn.<br>Method |
|--------|--|-------------|--------|-----------------|---------------|----------------|
| 425    |  | C25H26N4O8  | 510.51 | 8.25 (1)<br>98% | 511           | 1              |
| 426    |  | C21H30N4O7  | 450.50 | 8.0 (1)<br>98%  | 451           | 2              |
| 427    |  | C20H24N4O8S | 480.50 | 7.87 (1)<br>98% | 481           | 3              |

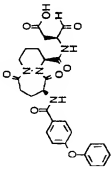
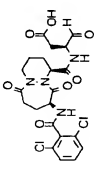
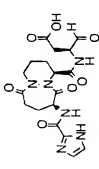
| Compd. | Structure  | MF          | MW     | HPLC RT<br>min  | MS<br>(M+H) <sup>+</sup> | Syn.<br>Method |
|--------|--|-------------|--------|-----------------|--------------------------|----------------|
| 428    |  | C16H25N5O8S | 447.47 | 5.13 (1)<br>98% | 448                      | 3              |
| 429    |  | C14H20N4O6  | 340.34 | 3.19 (3)<br>98% | 341                      |                |
| 430    |  | C23H27N5O8  | 501.50 | 5.53 (1)<br>98% | 502                      | 1A             |
| 431    |  | C21H25N5O7  | 459.46 | 6.66 (2)<br>98% | 460                      | 1              |

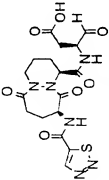
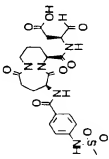
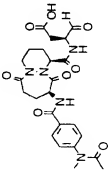
| Cmpd. | Structure  | MF         | MW     | HPLC RT<br>min   | MS<br>(M+H) <sup>+</sup> | Syn.<br>Method |
|-------|--|------------|--------|------------------|--------------------------|----------------|
| 432   |  | C21H23N7O7 | 485.46 | 5.59 (1)<br>98%  | 486                      | 1              |
| 433   |  | C24H27N5O7 | 497.51 | 11.07 (1)<br>97% | 498                      | 1              |
| 434   |  | C22H24N6O7 | 484.47 | 4.43 (1)<br>98%  | 485                      | 1              |
| 435   |  | C24H25N5O7 | 495.50 | 5.10 (1)<br>98%  | 496                      | 1              |

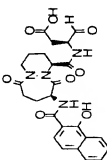
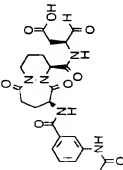
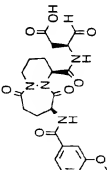
| Cmpd. | Structure  | MF         | MW     | HPIC Rt<br>min   | MS<br>(M+H) <sup>+</sup> | Syn.<br>Method |
|-------|--|------------|--------|------------------|--------------------------|----------------|
| 436   |  | C24H25N5O7 | 495.50 | 8.20 (4)<br>98%  | 496                      | 1              |
| 437   |  | C25H27N5O8 | 525.52 | 12.78 (5)<br>98% | 526                      | 1              |
| 438   |  | C24H25N5O7 | 495.50 | 4.85 (1)<br>98%  | 496                      | 1              |
| 439   |  | C24H25N5O7 | 495.50 | 8.70 (5)<br>98%  | 496                      | 1              |

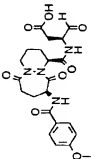
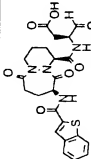
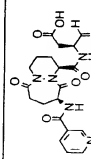
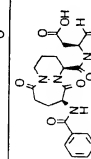


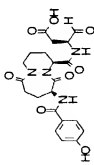
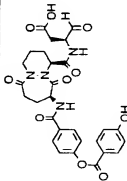
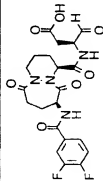
| Compd. | Structure  | MF           | MW     | HPLC RT<br>min   | MS<br>(M+H) <sup>+</sup> | Syn.<br>Method |
|--------|--|--------------|--------|------------------|--------------------------|----------------|
| 440    |  | C25H27N5O7   | 509.52 | 9.96 (5)<br>98%  | 510                      | 1              |
| 441    |  | C27H31N5O7   | 537.58 | 6.15 (1)<br>98%  | 538                      | 1              |
| 442    |  | C21H22N4O7S2 | 506.56 | 10.10 (1)<br>98% | 507                      | 1              |

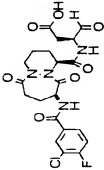
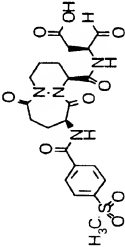
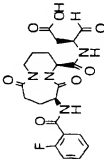
| Compd. | Structure  | MF  | MW     | HPLC RT<br>min   | MS<br>(M+H) <sup>+</sup> | Syn.<br>Method |
|--------|--|---|--------|------------------|--------------------------|----------------|
| 443    |  | C <sub>27</sub> H <sub>28</sub> N <sub>4</sub> O <sub>8</sub>                 | 536.55 | 13.12 (1)<br>98% | 537                      | 1              |
| 444    |  | C <sub>21</sub> H <sub>22</sub> Cl <sub>2</sub> N <sub>4</sub> O <sub>7</sub> | 513.34 | 9.96 (5)<br>98%  | 510                      | 1              |
| 445    |  | C <sub>18</sub> H <sub>22</sub> N <sub>6</sub> O <sub>7</sub>                 | 434.41 | 5.72 (1)<br>98%  | 435                      | 5              |

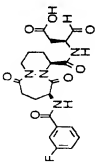
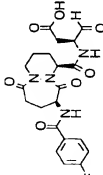
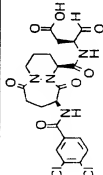
| Compd. | Structure  | MF          | NW     | HPLC RT<br>min  | MS<br>(M+H) + | Syn.<br>Method |
|--------|--|-------------|--------|-----------------|---------------|----------------|
| 446    |  | C17H20N6O7S | 452.45 | 5.00 (1)<br>98% | 453           | 1              |
| 447    |  | C22H27N5O9S | 537.55 | 6.32 (1)<br>98% | 538           | 1B             |
| 448    |  | C24H29N5O8  | 515.53 | 6.36 (1)<br>98% | 516           | 1A             |

| Compd. | Structure  | MF  | MW     | HPLC RT<br>min   | MS<br>(M+H) <sup>+</sup> | Syn.<br>Method |
|--------|--|---|--------|------------------|--------------------------|----------------|
| 449    |  | C <sub>25</sub> H <sub>26</sub> N <sub>4</sub> O <sub>8</sub> | 510.51 | 13.86 (1)<br>98% | 511                      | 1              |
| 450    |  | C <sub>23</sub> H <sub>27</sub> N <sub>5</sub> O <sub>8</sub> | 501.50 | 6.10 (1)<br>98%  | 502                      | 1A             |
| 451    |  | C <sub>22</sub> H <sub>26</sub> N <sub>4</sub> O <sub>8</sub> | 474.47 | 8.02 (1)<br>98%  | 475                      | 2              |

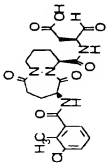
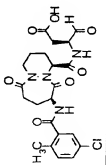
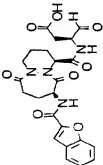
| Cmpd. | Structure  | MF           | MW     | HPLC RT<br>min   | MS<br>(M+H) <sup>+</sup> | Syn.<br>Method |
|-------|--|--------------|--------|------------------|--------------------------|----------------|
| 452   |  | C22H26N4O8   | 474.47 | 7.77 (1)<br>98%  | 475                      | 2              |
| 453   |  | C23H24N4O7S  | 500.53 | 11.11 (1)<br>98% | 501                      | 2              |
| 454   |  | C20H23N5O7   | 445.44 | 6.24 (2)<br>98%  | 446                      | 2              |
| 455   |  | C21H23ClN4O7 | 478.89 | 9.45 (1)<br>98%  | 479                      | 2              |

| Cmpd. | Structure  | MF           | MW     | HPLC RT<br>min   | MS<br>(M+H) <sup>+</sup> | Syn.<br>Method |
|-------|--|--------------|--------|------------------|--------------------------|----------------|
| 456   |  | C21H24N4O8   | 460.45 | 5.58 (1)<br>98%  | (M+Na)<br>483            | 1              |
| 457   |  | C28H28N4O10  | 580.56 | 10.42 (1)<br>98% | (M+Na)<br>603            | 1              |
| 458   |  | C21H22F2N4O7 | 480.43 | 8.65 (1)<br>98%  | (M+Na)<br>481.1          | 1              |

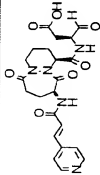
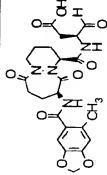
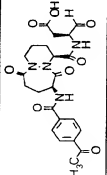
| Cmpd. | Structure  | MF            | MW     | HPLC RT<br>min   | MS<br>(M+H) <sup>+</sup> | Syn.<br>Method |
|-------|--|---------------|--------|------------------|--------------------------|----------------|
| 459   |  | C21H22ClFN4O7 | 496.88 | 10.11 (1)<br>98% | 498.3                    | 1              |
| 460   |  | C22H26N4O9S   | 522.54 | 6.16 (1)<br>98%  | 523.6                    | 1              |
| 461   |  | C21H23FN4O7   | 462.44 | 7.41 (1)<br>98%  | 463.3                    | 1              |

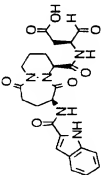
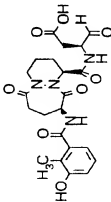
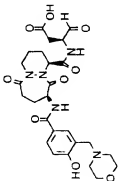
| Compd. | Structure  | MF  | MW     | HPLC RT<br>min   | MS<br>(M+H) <sup>+</sup> | Syn.<br>Method |
|--------|--|---|--------|------------------|--------------------------|----------------|
| 462    |  | C <sub>21</sub> H <sub>23</sub> FN <sub>4</sub> O <sub>7</sub>                | 462.44 | 7.71 (1)<br>98%  | 463.3                    | 1              |
| 463    |  | C <sub>21</sub> H <sub>23</sub> FN <sub>4</sub> O <sub>7</sub>                | 462.44 | 7.64 (1)<br>98%  | 464                      | 1              |
| 464    |  | C <sub>21</sub> H <sub>22</sub> Cl <sub>2</sub> N <sub>4</sub> O <sub>7</sub> | 513.34 | 11.59 (1)<br>98% | 414.5                    | 1              |

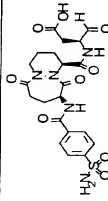
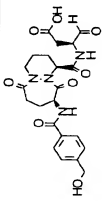
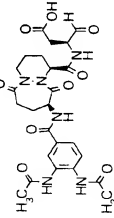


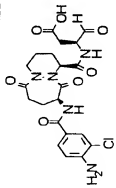
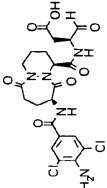
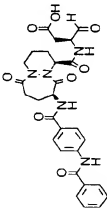
| Compd. | Structure  | MF  | MW     | HPLC RT<br>min  | MS<br>(M+H) <sup>+</sup> | Syn.<br>Method |
|--------|--|---|--------|-----------------|--------------------------|----------------|
| 465    |  | C <sub>22</sub> H <sub>25</sub> ClN <sub>4</sub> O <sub>7</sub> | 492.92 | 9.65 (1)<br>98% | 493.9                    | 1              |
| 466    |  | C <sub>22</sub> H <sub>25</sub> ClN <sub>4</sub> O <sub>7</sub> | 492.92 | 9.63 (1)<br>98% | 493.9                    | 1              |
| 467    |  | C <sub>23</sub> H <sub>24</sub> N <sub>4</sub> O <sub>8</sub>   | 484.47 | 9.73 (1)<br>98% | 485.8                    | 1              |

| Cmpd. | Structure | MF            | MW     | HPLC RT<br>min   | MS<br>(M+H) <sup>+</sup> | Syn.<br>Method |
|-------|-----------|---------------|--------|------------------|--------------------------|----------------|
| 468   |           | C26H26F3N5O7S | 609.59 | 14.84 (1)<br>98% | 609.7                    | 1              |
| 470   |           | C23H29N5O7    | 487.52 | 4.57 (1)<br>98%  | 489.5                    | 1              |
| 471   |           | C23H29N5O7    | 487.52 | 5.74 (1)<br>98%  | 488.2                    | 1              |

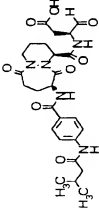
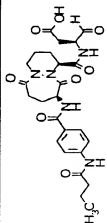
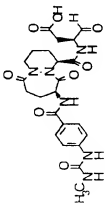
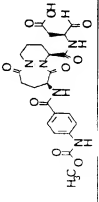
| Cmpd. | Structure  | MF         | MW     | HPLC RT<br>min  | MS<br>(M+H) <sup>+</sup> | Syn.<br>Method |
|-------|--|------------|--------|-----------------|--------------------------|----------------|
| 472   |  | C22H25N5O7 | 471.47 | 4.00 (1)<br>98% | 474                      | 1              |
| 473   |  | C23H26N4O9 | 502.49 | 7.65 (1)<br>98% | 503.6                    | 1              |
| 474   |  | C23H26N4O8 | 486.49 | 7.16 (1)<br>98% | 488.1                    | 1              |

| Compd. | Structure  | MF         | MW     | HPLC RT<br>min  | MS<br>(M+H) <sup>+</sup> | Syn.<br>Method |
|--------|--|------------|--------|-----------------|--------------------------|----------------|
| 475    |  | C23H25N5O7 | 483.49 | 9.77 (1)<br>97% | 485.1                    | 1              |
| 476    |  | C22H26N4O8 | 474.47 | 5.25 (1)<br>98% | 475.8                    | 1              |
| 477    |  | C26H33N5O9 | 559.58 | 4.76 (1)<br>95% | 561.8                    | 1              |

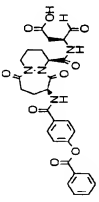
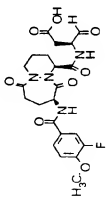
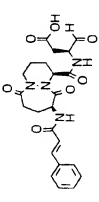
| Cmpd. | Structure  | MF          | MW     | HPLC RT<br>min  | MS<br>(M+H) | Syn.<br>Method |
|-------|--|-------------|--------|-----------------|-------------|----------------|
| 478   |  | C21H25N5O9S | 523.53 | 5.25 (1)<br>98% | 524.3       | 1              |
| 479   |  | C22H26N4O8  | 474.47 | 5.35 (1)<br>98% | 475.8       | 1              |
| 480   |  | C25H30N6O9  | 558.55 | 5.11 (1)<br>98% | 559.3       | 1A             |

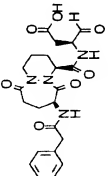
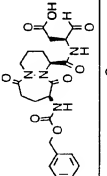
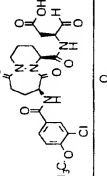
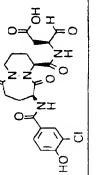
| Compd. | Structure  | MF  | MW     | HPLC RT<br>min   | MS<br>(M+H) <sup>+</sup> | Syn.<br>Method |
|--------|--|---|--------|------------------|--------------------------|----------------|
| 481    |  | C <sub>21</sub> H <sub>24</sub> ClN <sub>5</sub> O <sub>7</sub>               | 493.9  | 7.10 (1)<br>98%  | 495.1                    | 1              |
| 482    |  | C <sub>21</sub> H <sub>23</sub> Cl <sub>2</sub> N <sub>5</sub> O <sub>7</sub> | 528.4  | 9.05 (1)<br>98%  | 529.8                    | 1              |
| 483    |  | C <sub>28</sub> H <sub>29</sub> N <sub>5</sub> O <sub>8</sub>                 | 563.57 | 10.01 (1)<br>98% | 565.6                    | 1,2            |

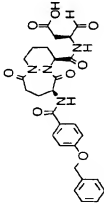
| Cmpd. | Structure | MF         | MW     | HPLC RT<br>min   | MS<br>(M+H) + | Syr.<br>Method |
|-------|-----------|------------|--------|------------------|---------------|----------------|
| 484   |           | C25H31N5O8 | 529.55 | 7.88 (1)<br>98%  | 531           | 1, 2           |
| 485   |           | C24H29N5O8 | 515.53 | 7.00 (1)<br>98%  | 517.6         | 1, 2           |
| 486   |           | C29H31N5O8 | 577.60 | 10.43 (1)<br>98% | 579.4         | 1, 2           |

| Cmpd. | Structure  | MF         | MW     | HPLC RT<br>min  | MS<br>(M+H) <sup>+</sup> | Syn.<br>Method |
|-------|--|------------|--------|-----------------|--------------------------|----------------|
| 487   |  | C26H33N5O8 | 543.58 | 9.30 (1)<br>98% | 545.7                    | 1, 2           |
| 488   |  | C25H31N5O8 | 529.55 | 8.13 (1)<br>98% | 531.1                    | 1, 2           |
| 489   |  | C23H28N6O8 | 516.52 | 5.89 (1)<br>98% | 517.8                    | 1, 4           |
| 490   |  | C23H27N5O9 | 517.50 | 7.27 (1)<br>98% | (M+Na)<br>540.8          | 1, 2           |



| Compd. | Structure  | MF          | MW     | HPLC RT<br>min  | MS<br>(M+H) <sup>+</sup> | Syn.<br>Method |
|--------|--|-------------|--------|-----------------|--------------------------|----------------|
| 491    |  | C28H28N4O9  | 564.56 | 12.9 (1)<br>98% | 565.3                    | 1              |
| 493    |  | C22H25FN4O8 | 492.46 | 8.31 (1)<br>98% | 493.9                    | 1              |
| 494    |  | C23H26N4O7  | 470.49 | 9.34 (1)<br>98% | 471.2                    | 2              |

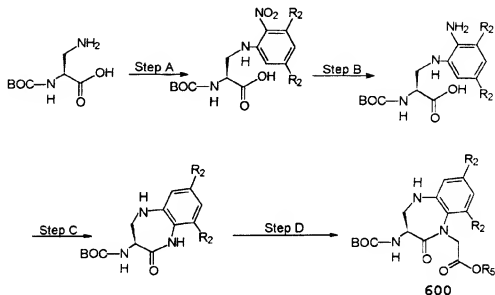
| Compd. | Structure  | MF  | MW     | HPLC RT<br>min  | MS<br>(M+H) <sup>+</sup> | Syn.<br>Method |
|--------|--|---|--------|-----------------|--------------------------|----------------|
| 495    |  | C <sub>22</sub> H <sub>26</sub> N <sub>4</sub> O <sub>7</sub>   | 458.48 | 7.24 (1)<br>98% | 459.9                    | 2              |
| 496    |  | C <sub>22</sub> H <sub>26</sub> N <sub>4</sub> O <sub>8</sub>   | 474.47 | 9.47 (1)<br>98% | 475.7                    | 2              |
| 497    |  | C <sub>22</sub> H <sub>25</sub> ClN <sub>4</sub> O <sub>8</sub> | 508.92 | 9.58 (1)<br>98% | 509.5                    | 1              |
| 498    |  | C <sub>21</sub> H <sub>23</sub> ClN <sub>4</sub> O <sub>8</sub> | 494.89 | 7.18 (1)<br>98% | 495.1                    | 1              |

| Compd. | Structure  | MF         | MW     | HPLC RT<br>min   | MS<br>(M+H) <sup>+</sup> | Syn.<br>Method |
|--------|--|------------|--------|------------------|--------------------------|----------------|
| 499    |  | C28H30N4O8 | 550.57 | 13.27 (1)<br>98% | 552                      | 1              |

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Example 12

Compounds **605a-j**, **605m-q**, **605s**, **605t**, and **605v** were synthesized as described below.



5

| Compound no.    | R <sub>2</sub>  | R <sub>5</sub>     |
|-----------------|-----------------|--------------------|
| <b>600a/103</b> | H               | CH <sub>3</sub>    |
| <b>600b</b>     | H               | CH <sub>2</sub> Ph |
| <b>600c</b>     | CH <sub>3</sub> | CH <sub>2</sub> Ph |

(3*S*)-2-Oxo-3-*tert*-butoxycarbonylamino-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetic acid methyl ester (**600a/103**).

**Step A.** (2*S*)-2-*tert*-Butoxycarbonylamino-3-(2-nitrophenyl-amino)-propionic acid. (2*S*)-2-*tert*-Butoxycarbonylamino-3-aminopropionic acid (10 g, 49 mmol), 2-fluoronitrobenzene (5.7 ml, 54 mmol), and NaHCO<sub>3</sub> (8.25 g, 98 mmol) was taken into 130 ml of DMF

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and heated at 80 °C for 18 h. The reaction was evaporated *in vacuo* to give a viscous orange residue that was dissolved in 300 ml of H<sub>2</sub>O and extracted with Et<sub>2</sub>O (3 x 150 ml). The aq. solution was acidified to pH 5 with 10% NaHSO<sub>4</sub> and extracted with EtOAc (3 x 250 ml). The combined extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated to give 12.64 g (83%) of the title compound as an orange amorphous solid: <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 8.15-8.10 (1H,d), 7.54-7.48 (1H,t), 7.13-7.08 (1H, d), 6.73-6.65 (1H, t), 4.45-4.35 (1H, m), 3.9-3.8 (1H, dd), 3.65-3.55 (1H, dd), 1.45 (9H, s).

**Step B. (2S)-2-tert-Butoxycarbonylamino-3-(2-aminophenyl-amino)-propionic acid.** A mixture of (2S)-2-tert-Butoxycarbonylamino-3-(2-nitrophenylamino)propionic acid (12.65 g, 40.5 mmol) and 0.5 g of 10% Pd/C in 100 ml of MeOH under hydrogen at 1 atmosphere was stirred for 4 h. The solution was filtered through Celite 545 and the filtrate evaporated *in vacuo* to afford the 11.95 g of the title compound in quantitative yield as a dark brown solid that was used without purification: <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 6.75-6.70 (3H,m), 6.65-6.58 (1H, m), 4.35-4.3 1H, m), 3.6-3.38 (2H, m), 1.45 (9H, s).

**Step C. (3S)-2-Oxo-3-tert-Butoxycarbonylamino-1,3,4,5-tetrahydro-1H-1,5-benzodiazepine.** 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (8.54 g, 44.5 mmol) was added to a cooled (0 °C) solution of (2S)-2-tert-butoxycarbonylamino-3-(2-aminophenylamino)propionic acid (11.95 g, 40.5 mmol) in 100 ml of DMF and stirred for 18 h. The reaction was poured into 700 ml of EtOAc and washed four times with

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- 100 ml of H<sub>2</sub>O. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated to give a brown solid that was purified by flash chromatography eluting with 3:7 EtOAc/hexane to give 8 g (71%) of the
- 5 title compound: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.78 (1H, s), 7.02-6.95 (1H, m), 6.88-6.82 (1H, m), 6.82-6.78 (1H, m), 6.75-6.70 (1H, m), 5.8-5.7 (1H, d), 4.55-4.45 (1H, m), 3.95 (1H, s), 3.9-3.82 (1H, m), 3.48-3.40 (1H, m), 1.45 (9H, s).
- 10 **Step D.** (3S)-2-Oxo-3-tert-butoxycarbonylamino-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester (600a/103). A 1.0 M solution of lithium bis(trimethylsilyl)amide (3.4 ml, 3.4 mmol) in THF was added dropwise to a -78 °C solution of (3S)-2-oxo-3-
- 15 tert-butoxycarbonylamino-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine (0.94 g, 3.38 mmol) in 20 ml of anhydrous THF and stirred for 30 min. Methyl bromoacetate (0.44 ml, 4 mmol) was added dropwise to the reaction mixture then warmed to RT. The reaction
- 20 was diluted with 100 ml of EtOAc and washed with 0.3N KHSO<sub>4</sub> (50 ml), H<sub>2</sub>O (2 x 50 ml), and brine. The combined organics were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated to afford a gum that was purified by flash chromatography eluting with 3:7
- 25 EtOAc/Hex. to give 0.98 g (83%) of the title compound as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.15-7.07 (2H, m), 6.98-6.94 (1H, m), 6.88-6.84 (1H, d), 5.62-5.55 (1H, d), 4.71-4.65 (1H, d), 4.65-4.6 (1H, m), 4.33-4.27 (1H, d), 3.96-3.90 (1H, m), 3.78 (3H, s), 3.44-3.37 (1H, m),
- 30 1.4 (9H, s).

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(3S)-2-Oxo-3-*tert*-butoxycarbonylamino-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (600b). Prepared by a similar method described for the preparation of 600a/103 (Step D), except benzyl bromoacetate was used instead of methyl bromoacetate to give 600b in quantitative yield.

(3S)-2-Oxo-3-*tert*-butoxycarbonylamino-2,3,4,5-tetrahydro-7,9-dimethyl-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (600c).

- 10 Step A. (2S)-2-*tert*-Butoxycarbonylamino-3-(2-nitro-3,5-dimethylphenylamino)-propionic acid. Prepared by a method similar as described for 600a/103 (Step A), except 2-fluoro-4,6-dimethyl-nitrobenzene was used instead of 2-fluoronitrobenzene to give the desired  
15 compound in 93% yield.

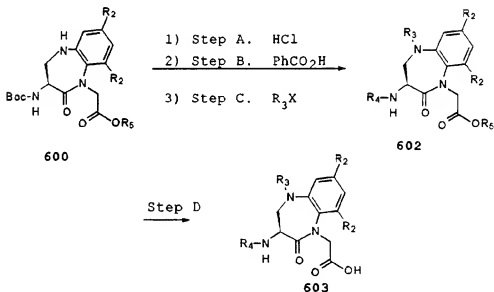
- Step B. (2S)-2-*tert*-Butoxycarbonylamino-3-(2-amino-3,5-dimethylphenyl-amino)-propionic acid. (2S)-2-*tert*-Butoxycarbonylamino-3-(2-nitro-3,5-dimethylphenyl-amino)propionic acid was converted to the title  
20 compound in quantitative yield as described in the preparation of 600a/103 (Step B).

- Step C. 2-Oxo-(3S)-3-*tert*-butoxycarbonylamino-2,3,4,5-tetrahydro-7,9-dimethyl-1H-1,5-benzodiazepine. A 0 °C solution of (2S)-2-*tert*-butoxycarbonylamino-3-(2-amino-3,5-dimethylphenyl-amino)-propionic acid (763 mg, 2.36  
25 mmol) and N-methylmorpholine (483 mg, 4.78 mmol) in 60 ml of anhydrous THF was treated dropwise with isobutylchloroformate (352 mg, 2.5 mmol). The reaction was stirred for 2 h at 0 °C, at RT for 1h and poured  
30 over EtOAc. The mixture was washed with aq. 5% NaHSO<sub>4</sub>,

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sat. aq.  $\text{NaHCO}_3$ , and sat. aq.  $\text{NaCl}$ , dried over  $\text{NaSO}_4$ , and concentrated *in vacuo*. Chromatography (flash,  $\text{SiO}_2$ , 10% to 25% to 50 %  $\text{EtOAc}/\text{CH}_2\text{Cl}_2$ ) gave 490 mg (68%) of the desired product.

- 5 **Step D.** (3*S*)-2-Oxo-3-*tert*-butoxycarbonylamino-2,3,4,5-tetrahydro-7,9-dimethyl-1*H*-1,5-benzodiazepine-1-acetic acid benzyl ester (600c). (2*S*)-2-*tert*-Butoxycarbonylamino-3-(2-amino-3,5-dimethylphenyl-amino)-propionic acid was converted to 600c, 75% by a  
10 similar method for the preparation of 600b.



(3*S*)-2-Oxo-3-benzoylamino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetic acid methyl ester (602a).

- Step A.** Anhydrous  $\text{HCl}$  was bubbled into a solution of  
15 (3*S*)-2-oxo-3-*tert*-butoxycarbonylamino-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetic acid methyl ester (600a/103, 4.0 g, 11.4 mmol) in 20 ml of  $\text{CH}_2\text{Cl}_2$  for 20 min then stirred for 1 h at RT. The reaction



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was evaporated to give (3S)-2-oxo-3-amino-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester hydrochloride as a white solid.

**Step B.** The white solid was dissolved in 70 ml of DMF and benzoic acid (1.5 g, 12.3 mmol) was added. The reaction was cooled in a ice/H<sub>2</sub>O bath and treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.4 g, 12.5 mmol), 1-hydroxybenzotriazole (1.7 g, 12.6 mmol) and diisopropylethylamine (3.0g, 23.2 mmol). The reaction was stirred for 18 h at RT under nitrogen atmosphere and poured onto H<sub>2</sub>O. The aq. mixture was extracted with EtOAc (2x). The combined organic layers were washed with aq. 0.5 N NaHSO<sub>4</sub>, H<sub>2</sub>O, sat. aq. NaHCO<sub>3</sub>, H<sub>2</sub>O and sat. aq. NaCl, dried over MgSO<sub>4</sub> and concentrated in vacuo. Chromatography (flash, SiO<sub>2</sub>, 10% to 30% EtOAc/CH<sub>2</sub>Cl<sub>2</sub>) gave 3.4 g (85%) of (3S)-2-oxo-3-(benzoylamino)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester as a white solid.

**Step C. Method A.** (3S)-2-Oxo-3-benzoylamino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester (602a). A solution of (3S)-2-oxo-3-(benzoylamino)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester (200 mg, 0.57 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 ml) was treated with triethylamine (119 mg, 1.13 mmol) and 3-phenylpropionyl chloride (114 mg, 0.68 mmol). The reaction was stirred at RT for 30 min and diluted with CH<sub>2</sub>Cl<sub>2</sub>. The solution was washed with aq. 10% HCl, sat. aq. NaHCO<sub>3</sub> and sat. aq. NaCl, dried over Na<sub>2</sub>SO<sub>4</sub> and

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concentrated *in vacuo* to give 240 mg (87%) of **602a** as a white foam.

- Step C. Method B. (3S)-2-Oxo-3-benzoylamino-5-acetoacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (602g).** A 0 °C solution of (3S)-2-oxo-3-(benzoylamino)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (**600b**) (465 mg, 1.10 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) was treated with acetoacetic acid in 1 ml of CH<sub>2</sub>Cl<sub>2</sub> followed by slow addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (431 mg, 2.2 mmol) in 2 ml of CH<sub>2</sub>Cl<sub>2</sub> under N<sub>2</sub> atmosphere. After 15 min the reaction was poured onto EtOAc, washed with aq. 5 % NaHSO<sub>4</sub>, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. Chromatography (flash, SiO<sub>2</sub>, 0% to 10% to 25% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) gave 580 mg of (3S)-2-oxo-3-(benzoylamino)-5-acetoacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzyl ester as a white solid.
- Step C. Method C. (3S)-2-Oxo-3-benzoylamino-5-methoxycarbonyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (602j).** A vigorously-stirred, 0 °C solution of (3S)-2-oxo-3-(benzoylamino)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (**600b**) (461 mg, 1.07 mmol) in THF (5 ml) and sat. aq. NaHCO<sub>3</sub> (2.5 ml) was treated with a THF solution (0.35 ml) of methyl chloroformate (151 mg, 1.6 mmol) and the reaction was stirred for 45 min at RT. The reaction was poured onto CH<sub>2</sub>Cl<sub>2</sub> and washed with H<sub>2</sub>O, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. Chromatography

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(flash, SiO<sub>2</sub>, 0% to 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) gave 525 mg of 602j as a white solid.

**Step C. Method D. (3S)-2-Oxo-3-benzoylamino-5-benzylaminocarbonyl-2,3,4,5-tetrahydro-1H-1,5-**

- 5 **benzodiazepine-1-acetic acid methyl ester (602p).** A solution of 600a/103 (400 mg, 1.1mmol) and benzylisocyanate (166 mg, 1.2mmol) in 10 ml of CH<sub>2</sub>Cl<sub>2</sub> and 10 ml of DMF and heated at 80 °C for 3 days. The reaction was cooled to RT poured onto H<sub>2</sub>O and extracted  
10 with EtOAc (2x). The combined organic layers were washed with H<sub>2</sub>O (4x) and sat. aq. NaCl, dried over MgSO<sub>4</sub> and concentrated *in vacuo*. Chromatography (flash, SiO<sub>2</sub>, 50% to 80% EtOAc/hexane) gave 440 mg (80%) of 602p as a white solid.

- 15 **Step C. Method E. (3S) 2-Oxo-3-benzylamino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester (602v).** A solution of (3S) 2-oxo-3-amino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid  
20 methyl ester hydrochloride (560 mg, 1.34 mmol), benzaldehyde (146 mg, 1.34 mmol) and sodium acetate (220 mg, 2.68 mmol) in methanol (20 ml) was treated with 4Å sieves (2 g) and NaCNBH<sub>3</sub> (168 mg, 2.68 mmol). The reaction was stirred for 2.5 h, acidified with 10%  
25 aq. HCl to pH 2 and washed with Et<sub>2</sub>O (2x75 ml). The organic layers were concentrated *in vacuo* to give an oil. Chromatography (flash, SiO<sub>2</sub>, 0 to 35% EtOAc/CH<sub>2</sub>Cl<sub>2</sub>) gave 250 mg (40%) of 602v as a clear oil.

- Step D. Method A. (3S)-2-Oxo-3-benzoylamino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-**  
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benzodiazepine-1-acetic acid (603a). (3S)-2-Oxo-3-benzoylamino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester (602a; 1.25 g, 2.57 mmol) was dissolved in 11 ml of

- 5 THF, MeOH and H<sub>2</sub>O (5:5:1) and treated with LiOH·H<sub>2</sub>O (42 mg, 0.62 mmol) stirred at RT for 64 h. The reaction was concentrated *in vacuo*, diluted with H<sub>2</sub>O and acidified with aq. 1N HCl to give 230 mg of 603a as a white solid.

- 10 Step D. Method B. (3S) 2-Oxo-3-benzoylamino-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid (603d). A mixture of (3S)-2-oxo-3-(benzoylamino)-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (602d; 510 mg, 1.08 mmol) and
- 15 5% Pd/C (250 mg) in MeOH (10 ml) stirred under H<sub>2</sub> (1 atm) for 0.5h. The reaction was filtered and concentrated *in vacuo* 410 mg of 603d as a white solid.

The compounds of Table 8 were prepared as described in Table 9, using the methods of Example 12.

20 Table 8

| Compound no. | R <sub>2</sub> | R <sub>3</sub>   | R <sub>4</sub> | R <sub>5</sub>     |
|--------------|----------------|--|----------------|--------------------|
| 602b         | H              | PhCH <sub>2</sub> C(O)                                 | PhC(O)         | CH <sub>2</sub> Ph |
| 602c         | H              | PhC(O)   | PhC(O)         | CH <sub>2</sub> Ph |
| 25 602d      | H              | CH <sub>3</sub> C(O)                                   | PhC(O)         | CH <sub>2</sub> Ph |
| 602e         | H              | CH <sub>3</sub> OCH <sub>2</sub> C(O)                  | PhC(O)         | CH <sub>2</sub> Ph |
| 602f         | H              | (CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub> C(O) | PhC(O)         | CH <sub>2</sub> Ph |
| 602g         | H              | CH <sub>3</sub> C(O)CH <sub>2</sub> C(O)               | PhC(O)         | CH <sub>2</sub> Ph |

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
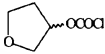
| Compound no. | R <sub>2</sub>  | R <sub>3</sub>  | R <sub>4</sub>                         | R <sub>5</sub>     |
|--------------|-----------------|---|--|--------------------|
| 602h         | H               | CH <sub>3</sub> OC(O)C(O)   | PhC(O)                                 | CH <sub>2</sub> Ph |
| 602i         | H               | CH <sub>3</sub> C(O)C(O)  | PhC(O)                                 | CH <sub>2</sub> Ph |
| 602j         | H               | CH <sub>3</sub> OC(O)   | PhC(O)                                 | CH <sub>2</sub> Ph |
| 602k         | H               | CH <sub>3</sub> C(O)  | Boc                                    | CH <sub>2</sub> Ph |
| 5 602l       | CH <sub>3</sub> | CH <sub>3</sub> C(O)  | Boc                                    | CH <sub>2</sub> Ph |
| 602m         | H               | CH <sub>3</sub> S(O <sub>2</sub> )  | PhC(O)                                 | CH <sub>3</sub>    |
| 602p         | H               | PhCH <sub>2</sub> NHC(O)  | PhC(O)                                 | CH <sub>3</sub>    |
| 602q         | H               |  | PhC(O)                                 | CH <sub>2</sub> Ph |
| 602r         | H               | PhCH <sub>2</sub> CH <sub>2</sub> C(O)  | PhCH <sub>2</sub> CH <sub>2</sub> C(O) | CH <sub>2</sub> Ph |
| 10 602s      | H               | 4-pyridylCH <sub>2</sub> C(O)   | PhC(O)                                 | CH <sub>2</sub> Ph |

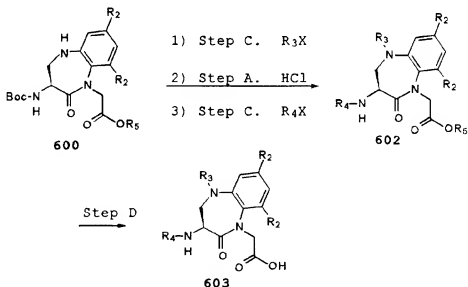
Table 9

| No.     | Starting material | R <sub>3</sub> X   | Step C method/<br>(% yield) | Step D method/<br>(% yield) |
|---------|-------------------|--|-----------------------------|-----------------------------|
| 603b    | 600b              | PhCH <sub>2</sub> C(O)Cl                                 | A (98)                      | B (89)                      |
| 603c    | 600b              | PhC(O)Cl   | A (quant.)                  | B (quant.)                  |
| 15 603d | 600b              | CH <sub>3</sub> C(O)Cl                                   | A (quant.)                  | B (quant.)                  |
| 603e    | 600b              | CH <sub>3</sub> OCH <sub>2</sub> C(O)Cl                  | A (59)                      | B (quant.)                  |
| 603f    | 600b              | (CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub> C(O)Cl | A (88)                      | B (95)                      |
| 603g    | 600b              | CH <sub>3</sub> C(O)CH <sub>2</sub> CO <sub>2</sub> H    | B (quant.)                  | B (quant.)                  |
| 603h    | 600b              | CH <sub>3</sub> OC(O)C(O)Cl                              | A (96)                      | B (quant.)                  |
| 20 603i | 600b              | CH <sub>3</sub> C(O)CO <sub>2</sub> H                    | B (87)                      | B (94)                      |
| 603j    | 600b              | CH <sub>3</sub> OC(O)Cl                                  | C (quant.)                  | B (quant.)                  |

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| No.  | Starting material | R <sub>3</sub> X   | Step C method/<br>(% yield) | Step D method/<br>(% yield) |
|------|-------------------|--|-----------------------------|-----------------------------|
| 603k | 600b              | CH <sub>3</sub> C(O)Cl   | A, Step C only<br>(quant.)  | not run                     |
| 603l | 600c              | CH <sub>3</sub> C(O)Cl   | A, Step C only<br>(quant.)  | not run                     |
| 603m | 600a/103          | CH <sub>3</sub> SO <sub>3</sub> Cl, NEt <sub>3</sub><br>instead of<br>pyridine and THF<br>instead of CH <sub>2</sub> Cl <sub>2</sub> | A (76)                      | A (92)                      |
| 603p | 600a/103          | PhCH <sub>2</sub> C=N=O  | D (80)                      | A (86)                      |
| 603q | 600b              |   | C (83)                      | B (71)                      |
| 603r | 600a/103          | PhCH <sub>2</sub> CH <sub>2</sub> C(O)Cl   | A                           |                             |
| 603s | 600b              | 4-pyridylCH <sub>2</sub> CO <sub>2</sub> H   | B (90)                      | B (98)                      |

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The compounds of Table 10 were prepared as described in Table 11 using the methods of Example 12.

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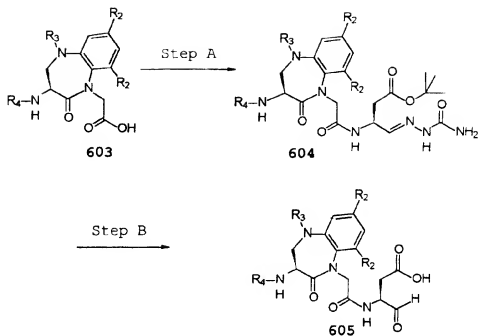
Table 10

| Compound no. | R <sub>2</sub>  | R <sub>3</sub>                           | R <sub>4</sub>     | R <sub>5</sub>     |
|--------------|-----------------|--|--------------------|--------------------|
| 602n         | H               | CH <sub>3</sub> C(O)                     | Naphthylene-2-C(O) | CH <sub>2</sub> Ph |
| 5 602o       | CH <sub>3</sub> | CH <sub>3</sub> C(O)                     | PhC(O)             | CH <sub>2</sub> Ph |
| 602t         | H               | 3-CH <sub>3</sub> PhCH <sub>2</sub> C(O) | PhC(O)             | CH <sub>2</sub> Ph |
| 602u         | H               | CH <sub>3</sub> C(O)                     | Fmoc               | CH <sub>2</sub> Ph |
| 602v         | H               | PhCH <sub>2</sub> CH <sub>2</sub> CO     | PhCH <sub>2</sub>  | CH <sub>3</sub>    |

Table 11

| No.     | Starting material | 1) Step C.<br>R <sub>3</sub> X method<br>(% yield)           | 3) Step C<br>R <sub>4</sub> X method<br>(% yield) | Step D<br>method<br>(% yield) |
|---------|-------------------|--|---|-------------------------------|
| 10 603n | 602k              | CH <sub>3</sub> C(O)Cl<br>A (quant.)                         | naphthylen<br>e-<br>2-C(O)Cl<br>A (70)            | B (quant.)                    |
| 603o    | 602l              | CH <sub>3</sub> C(O)Cl<br>A (quant.)                         | PhC(O)Cl<br>A (73)                                | B (quant.)                    |
| 603t    | 602k              | 3-<br>CH <sub>3</sub> PhCH <sub>2</sub> C(O)Cl<br>A (quant.) | PhC(O)Cl<br>A (93)                                | B (95)                        |
| 603u    | 602k              | CH <sub>3</sub> C(O)Cl<br>A (quant.)                         | Fmoc-Cl<br>C (82)                                 | C (98)                        |
| 15 603v | 600a/103          | PhCH <sub>2</sub> CH <sub>2</sub> C(O)Cl<br>A                | PhCHO<br>E (40)                                   | A (95)                        |

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
The compounds of Table 12 were prepared by the methods described below.

**Table 12**

| compound no. | $R_2$ | $R_3$                | $R_4$    |
|--------------|-------|----------------------|----------|
| 605a         | H     | $PhCH_2CH_2C(O)$     | $PhC(O)$ |
| 605b         | H     | $PhCH_2C(O)$         | $PhC(O)$ |
| 605c         | H     | $PhC(O)$             | $PhC(O)$ |
| 605d         | H     | $CH_3C(O)$           | $PhC(O)$ |
| 605e         | H     | $CH_3OCH_2C(O)$      | $PhC(O)$ |
| 605f         | H     | $(CH_3)_2CHCH_2C(O)$ | $PhC(O)$ |
| 605g         | H     | $CH_3C(O)CH_2C(O)$   | $PhC(O)$ |
| 605h         | H     | $CH_3OC(O)C(O)$      | $PhC(O)$ |
| 605i         | H     | $CH_3C(O)C(O)$       | $PhC(O)$ |
| 605j         | H     | $CH_3OC(O)$          | $PhC(O)$ |



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| compound no. | R <sub>2</sub>  | R <sub>3</sub>  | R <sub>4</sub>    |
|--------------|-----------------|---|-------------------|
| 605m         | H               | CH <sub>3</sub> SO <sub>3</sub>   | PhC(O)            |
| 605n         | H               | CH <sub>3</sub> C(O)  | Naphthyl-2-C(O)   |
| 605o         | CH <sub>3</sub> | CH <sub>3</sub> C(O)  | PhC(O)            |
| 605p         | H               | PhCH <sub>2</sub> NHC(O)  | PhC(O)            |
| 605q         | H               |  | PhC(O)            |
| 605s         | H               | 4-pyridylCH <sub>2</sub> C(O)   | PhC(O)            |
| 605t         | H               | 3-CH <sub>3</sub> PhCH <sub>2</sub> C(O)  | PhC(O)            |
| 605v         | H               | PhCH <sub>2</sub> CH <sub>2</sub> C(O)  | PhCH <sub>2</sub> |

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605a).

**Step A.** (3S)-3-(1-Fluorenylmethyloxycarbonylamino)-4-oxobutyric acid tert-butyl ester semicarbazone (210 mg, 0.45 mmol, Prepared in a similar manner to the benzyloxycarbonyl analog in Graybill et al., Int. J. Protein Res., 44, pp. 173-82 (1994).) was dissolved in 10 ml of DMF and 2 ml of diethylamine and stirred for 2 h. The reaction was concentrated in vacuo to give (3S)-3-amino-4-oxobutyric acid tert-butyl ester semicarbazone. The 0 °C solution of the above residue and 603a (200 mg, 0.42mmol) in 5 ml of DMF and 5 ml of CH<sub>2</sub>Cl<sub>2</sub> was treated with 1-hydroxybenzotriazole (57 mg, 0.42mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (98 mg, 0.51 mmol). The reaction was stirred at RT for 18 h, poured onto

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EtOAc (75 ml) and washed with aq. 0.3 N  $\text{KHSO}_4$ , sat. aq.  $\text{NaHCO}_3$  and sat. aq.  $\text{NaCl}$ , dried over  $\text{NaSO}_4$  and concentrated *in vacuo*. Chromatography (flash,  $\text{SiO}_2$ , 0% to 4%  $\text{MeOH}/0.1\% \text{NH}_4\text{OH}/\text{CH}_2\text{Cl}_2$ ) to give 240 mg (83%) of 604a.

**Step B.** 604a was stirred with 10 ml of 33%  $\text{TFA}/\text{H}_2\text{O}$  for 4 h and concentrated *in vacuo*. The residue was dissolved in 7 ml of  $\text{MeOH}/\text{acetic acid}/37\% \text{aq. formaldehyde}$  (5:1:1) and stirred for 18 h.

- 10 Chromatography (Reverse Phase C18, 4.4mm ID x 25 cm, 15% to 70%  $\text{CH}_3\text{CN}/0.1\% \text{TFA}/\text{H}_2\text{O}$ ) gave 32 mg (16%) of 605a as a white solid:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , existing as diastereomers of the hemiacetal)  $\delta$  7.85-7.78 (2H, d), 7.5-7.32 (6H, m), 7.32-7.28 (1H, m), 7.18-6.98 (5H, m),  
15 4.92-4.85 (2H, m), 4.5-4.32 (2H, m), 4.31-4.20 (2H, m), 3.7-3.6 (1H, m), 2.90-2.75 (2H, m), 2.65-2.5 (1H, m), 2.46-2.25 (3H, m).

The following compounds were prepared by a similar method:

- 20 (3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-phenylacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605b). 148 mg (33%) as a white solid:  $^1\text{H}$  NMR( $\text{CD}_3\text{OD}$ )  $\delta$  7.9-6.9 (m, 16H), 4.9 (s, 2H), 4.5 (m, 1H), 4.4 (m, 2H), 3.75 (s, 1H), 3.6  
25 (dd, 1H), 3.45 (dd, 1H), 2.7 (m, 1H), 2.5 (m, 1H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-benzoyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605c). 319 mg (56%) as a white solid:  $^1\text{H}$  NMR( $\text{CD}_3\text{OD}$ )  $\delta$  7.9-6.9 (m, 16H), 5.1 (m, 1H), 4.9 (dd,

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1H), 4.7 (m, 1H), 4.6 (dd, 1H), 4.4 (m, 2H), 4.05 (m, 1H), 2.7 (m, 1H), 2.5 (m, 1H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyr  
5 ic acid (605d). 190 mg (38%) as a white solid: <sup>1</sup>H NMR(CD<sub>3</sub>OD) δ 1.9(d, H), 2.4(m, 1H), 2.65(m, 1H), 3.7(m, 1H), 4.25(m, 1H), 4.45(m, 2H), 4.8-5.05(m, 3H), 7.3-7.7(m, 7H), 7.9(d, 2H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-methoxyacetyl-  
10 2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyr  
ic acid (605e). 250 mg (78%) <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 1.87 (bs), 1.95 (s, 2H), 2.1 (bs), 2.4 (m, 2H), 2.65 (m, 2H), 3.59 (bs), 3.75 (bs), 3.87 (bs), 4.19 (m), 4.37 (m), 4.50-4.78 (bm), 4.92 (m), 5.27  
15 (bs), 7.41-7.58 (m, 7H), and 7.87 ppm (d, 2H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-(3-methylbutyryl)-  
2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyr  
ic acid (605f). 210.5 mg (46%) as a white solid: <sup>1</sup>H NMR(CD<sub>3</sub>OD) δ 7.9-7.4 (m, 9H), 5.1  
20 (m, 1H), 4.9 (m, 1H), 4.6 (dd, 1H), 4.4 (m, 2H), 4.1 (d, 1H), 3.8 (m, 1H), 3.5 (q, 1H), 2.7 (m, 1H), 2.5 (m, 1H), 2.0 (m, 3H), 1.2 (t, 1H), 0.9 (d, 3H), 0.8 (d, 3H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-acetoacetyl-  
25 2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyr  
ic acid (605g). 81 mg (19%) as a white solid: <sup>1</sup>H NMR(CD<sub>3</sub>OD) δ 7.9-7.3 (m, 11H), 4.9-4.8 (m, 2H), 4.6-4.4 (m, 3H), 4.3 (m, 1H), 3.75 (q,

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1H), 3.55 (d, 1H), 2.7 (m, 1H), 2.5 (m, 1H), 2.05 (s, 3H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-methyloxalyl-  
2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-

5 acetylamino]4-oxo-butyric acid (605h). 227 mg (54%) of  
a white solid: <sup>1</sup>H NMR(CD<sub>3</sub>OD) δ 2.5 (m, 1H), 2.7 (m, 1H),  
3.55 (s, 3H), 3.8-4.0 (m, 2H), 4.4 (m, 1H), 4.6-4.8 (m,  
2H), 4.95 (d, 1H), 5.1 (m, 1H), 7.3-7.7 (m, 7H), 7.9 (d,  
2H), 8.6 (d, 1H).

10 (3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-acetylcarbonyl-  
2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-

acetylamino]4-oxo-butyric acid (605i). 150 mg (37%) as  
a white solid: <sup>1</sup>H NMR(CD<sub>3</sub>OD) δ 7.9-7.3 (m, 12H), 5.1  
(m, 1H), 4.65 (t, 1H), 4.55 (dd, 1H), 4.35 (m, 1H), 4.1  
15 (d, 1H), 3.9 (q, 1H), 3.45 (q, 1H), 2.7 (m, 1H), 2.5  
(m, 1H), 2.25 (s, 3H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-methoxycarbonyl-  
2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-

acetylamino]4-oxo-butyric acid (605j). 234 mg (44%) as  
20 a white solid: <sup>1</sup>H NMR(CD<sub>3</sub>OD) δ 7.9-7.4 (m, 12H), 5.0  
(m, 1H), 4.8-4.5 (m, 3H), 4.4 (m, 1H), 4.3 (t, 1H),  
3.9-3.75 (m, 2H), 3.6 (s, 3H), 2.7 (m, 1H), 2.5 (m,  
1H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-methanesulfonyl-  
25 2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-

acetylamino]4-oxo-butyric acid (605m). 64.5 mg (34%)  
as a white solid: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, exisiting as  
diastereomers of the hemiacetal & open form of the  
aldehyde) δ 9.48 (0.2H, s), 8.85-8.72 (1H, m), 8.65-

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8.60 (0.8 H, d), 8.30-8.26 (0.2 H, d), 7.95-7.88 (2H, d), 7.6-7.45 (6H, m), 7.44-7.38 (1H, m), 5.78-5.75 (0.2H, d), 5.48 (0.6H, s), 4.85-4.70 (2H, m), 4.62-4.54 (1H, d), 4.50-4.40 (2H, m), 4.25-4.14 (1H, m), 3.9-3.85 (1H, m), 3.16 (3H, s), 3.05-2.3 (2, m).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-(naphthlene-2-carbonyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetyl amino]4-oxo-butyric acid (605n). 103 mg (17%) as a white solid: <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 1.9(s, 3H), 2.5(m, 1H), 2.65(m, 1H), 3.75(m, 1H), 4.3(m, 1H), 4.5-4.7(m, 3H), 4.85-5.1(m, 2H), 7.3-7.65(m, 6H), 7.85-8.05(m, 4H), 8.45(s, 1H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-acetyl-2,3,4,5-tetrahydro-7,9-dimethyl-1H-1,5-benzodiazepin-1-acetyl amino]4-oxo-butyric acid (605o). 42 mg (12%) as a white solid: <sup>1</sup>H NMR (CD<sub>3</sub>OD, existing as diastereomers of the hemiacetal) δ 7.85-7.74 (2H, m), 7.5-7.44 (1H, m), 7.43-7.35 (4H, m), 5.6-5.05 (2H, m), 4.82-4.42 (2H, m), 4.40-3.95 (2H, m), 3.6-3.5 (1H, m), 2.7-2.38 (2H, m), 2.32 (3H, s), 2.27 (3H, s), 1.92 (3H, s).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-benzylaminocarbonyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetyl amino]4-oxo-butyric acid (605p). 165 mg (37%) as a white solid: <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 2.45(m, 1H), 2.7(m, 1H), 3.8(m, 1H), 4.15-4.5(m, 4H), 4.5-4.75(m, 2H), 4.8-5.0(m, 2H), 7.1-7.7(m, 12H), 7.9(d, 2H).

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(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-[(3R,S) 3-tetrahydrofuran-2-ylmethoxycarbonyl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyr-  
ic acid (605q). 210 mg (66%) <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 1.95 (s, 2H),

2.4 (m, 2H), 2.65 (m, 2H), 3.29 (s, 3H), 3.78 (m), 3.87 (bs), 4.0 (d, 1H), 4.32 (m), 4.50-4.15 (m), 4.95 (m), 5.27 (bs), 7.45-7.65 (m, 7H), and 7.69 ppm (d, 2H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-(4-pyridylacetyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-

acetylamino]4-oxo-butyr-  
ic acid (605s). 128 mg (19%) as a white solid: <sup>1</sup>H NMR(CD<sub>3</sub>OD) δ 8.5-7.4 (m, 13H), 5.0 (m, 1H), 4.7 (m, 1H), 4.5 (m, 2H), 4.45-4.4 (m, 3H), 3.8-3.7 (m, 2H), 2.7 (m, 1H), 2.5 (m, 1H).

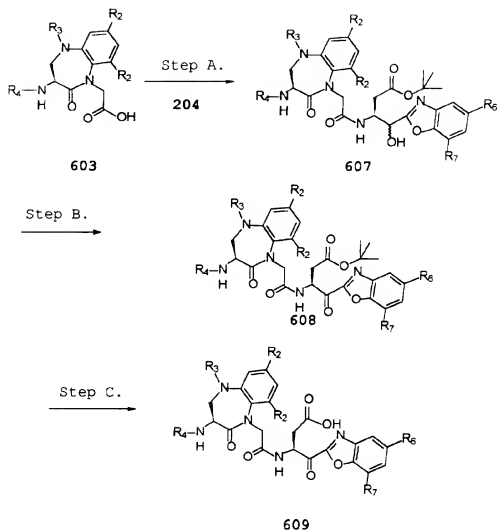
(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-(3-

methylphenylacetyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyr-  
ic acid (605t). 132 mg (24%) as a white solid: <sup>1</sup>H NMR(CD<sub>3</sub>OD) δ 7.8-6.7 (m, 13H), 4.9 (t, 1H), 4.75 (dd, 1H), 4.2 (dd, 1H), 4.1 (m, 2H), 3.8 (dd, 1H), 3.6 (q, 1H), 3.45 (dd, 1H), 3.3 (dd, 1H), 2.6 (m, 1H), 2.3 (m, 1H), 2.15 (s, 3H).

(3S) 3-[(3S) 2-Oxo-3-benzylamino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyr-  
ic acid trifluoroacetic acid salt (605v). 88 mg (28%) as a white solid: <sup>1</sup>H NMR

(CD<sub>3</sub>OD) δ 7.63-7.51 (2H, m), 7.5-7.35 (7H, m), 7.25-7.10 (3H, m), 7.1-7.02 (2H, m), 5.04-4.96 (1H, m), 4.75-4.57 (2H, m), 4.38-4.15 (2H, m), 4.24-4.12 (2H, m), 4.10-4.02 (1H, d), 4.88-4.75 (1H, m), 2.90-2.80 (2H, m), 2.78-2.63 (1H, m), 2.55-2.35 (2H, m), 2.34-2.22 (1H, m).

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The compounds of Table 13 are described below.

**Table 13**

| #    | R <sub>2</sub> | R <sub>3</sub>                         | R <sub>4</sub>                         | R <sub>6</sub> | R <sub>7</sub> |
|------|----------------|--|--|----------------|----------------|
| 609a | H              | PhCH <sub>2</sub> CH <sub>2</sub> C(O) | PhCH <sub>2</sub> CH <sub>2</sub> C(O) | Cl             | Cl             |
| 609b | H              | CH <sub>3</sub> C(O)                   | PhC(O)                                 | Cl             | Cl             |

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(3S)-3-[(3S)-2-Oxo-3-(3-phenylpropionylamino)-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]-4-(5,7-dichlorobenzoxazol-2-yl)-4-oxo-butyric acid (609a).

5 **Step A.** A solution of 204 (223 mg, 0.5 mmol) and 603r (300mg; 0.36 mmol) in 4 ml of DMF and 4 ml of CH<sub>2</sub>Cl<sub>2</sub> was treated with (Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub> (10 mg), 1-hydroxybenzotriazole (135 mg, 1.0 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride  
10 (115 mg, 0.6 mmol). Tri-n-butyl tin hydride (219 mg, 0.75 mmol) was added dropwise to the reaction and stirred for 18 h. The reaction was poured onto EtOAc and washed with aq. 10% NaHSO<sub>4</sub>, sat. aq. NaHCO<sub>3</sub> and sat. aq. NaCl, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. Chromatography (flash, SiO<sub>2</sub>, 0% to 50%  
15 EtOAc/hexane) gave 360 mg (86%) of 607a as a foam.

**Step B.** A solution of 607a (360 mg) in 5 ml of CH<sub>2</sub>Cl<sub>2</sub> was added dropwise to a suspension of 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodioxol-3(1H)-one (362 mg, 0.85  
20 mmol) in 20 ml of CH<sub>2</sub>Cl<sub>2</sub>. The reaction was stirred for 4.5 h, diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with a 1:1 mixture of sat. aq. NaHCO<sub>3</sub>/sat. aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, sat. aq. NaHCO<sub>3</sub> (2x) and sat. aq. NaCl, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. Chromatography (flash, SiO<sub>2</sub>,  
25 20% EtOAc/CH<sub>2</sub>Cl<sub>2</sub>) gave 340 mg (95%) of the ketone 608a.

**Step C.** 608a (300 mg, 0.36 mmol) was dissolved in 25 ml of 25% TFA/CH<sub>2</sub>Cl<sub>2</sub> and stirred at RT for 5 h and concentrated *in vacuo*. Chromatography (flash, SiO<sub>2</sub>, 0 to 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) gave 118 mg (42%) of 609a as a white  
30 solid: <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.62-6.65 (16H, m), 4.85-4.7

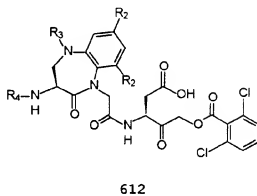
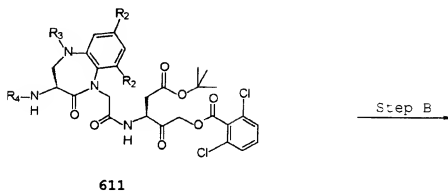
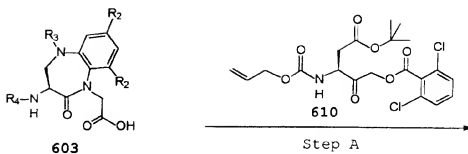


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(1H, m), 4.68-4.42 (2H, m), 4.40-4.15 (2H, m), 3.48-3.28 (1H, m), 3.0-2.9 (1H, m), 2.9-2.6 (4H, m), 2.55-2.18 (3H, m), 2.16-1.96 (2H, m).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]-4-(5,7-dichlorobenzoxazol-2-yl)-4-oxo-butyric acid (609b) was prepared from 603d in a similar manner as 609a to give 287 mg (43% overall yield) as white solid: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.6(s, 3H), 2.7-3.1(m, 2H), 3.45(m, 1H), 4.4(t, 1H), 4.7(m, 2H), 4.95(m, 1H), 5.2, 5.4(2s, 1H), 7.2-7.65(m, 8H), 7.9(d, 2H), 8.8(t, 1H), 8.9,9.1(2s, 1H), 12.6(br, 1H).

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(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-methanesulfonyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylaminol]-5-(2,6-dichlorobenzoyloxy)-4-oxopentanoic acid (612) was prepared by a method similar as 607a

5 (Steps A and C only) using 603m (150 mg, 0.36 mmol)

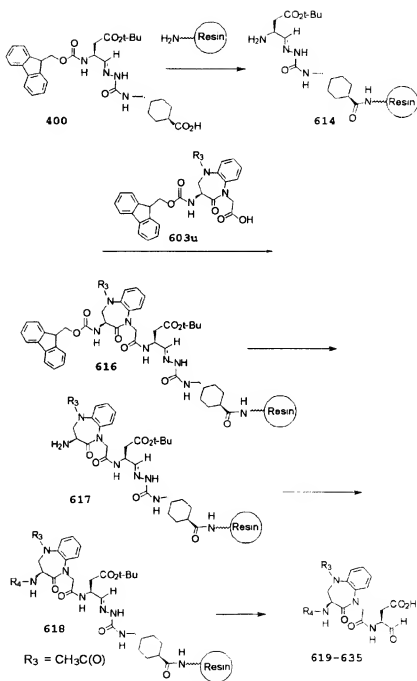
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instead of **603r** and (3S)-3-(allyloxycarbonylamino)-4-oxo-5-(2,6-dichlorobenzoyl-oxy)pentanoic acid *t*-butyl ester (110; 160 mg, 0.36 mmol, WO 93/16710) instead of **606a** to give **612** (56%) as a white solid: <sup>1</sup>H NMR  
5 (CDCl<sub>3</sub>) 7.85-7.10 (12H, m), 5.4-4.65 (4H, m), 4.6-4.15 (4H, m), 3.10-2.72 (5H, s & m).

### Example 13

Compounds **619-635** were synthesized as described in Example 13 and Table 14.

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**Syntheses of 619-635.**

**Step A. Synthesis of 614.** TentaGel S $\phi$  NH<sub>2</sub> resin (0.16 mmol/g, 10.0 g) was placed in a sintered glass funnel and washed with dimethylformamide (3 X 50 mL),  
5 10% (v/v) diisopropylethylamine (DIEA) in dimethylformamide (2 X 50 mL) and finally with dimethylformamide (4 X 50 mL). Sufficient dimethylformamide was added to the resin to obtain a slurry followed by **400** (1.42 g, 2.4 mmol, prepared from  
10 (3S) 3-(fluorenylmethoxycarbonyl)-4-oxobutryic acid t-butyl ester according to A.M. Murphy et. al. J. Am. Chem. Soc., 114, 3156-3157 (1992)), 1-hydroxybenzotriazole hydrate (HOBt·H<sub>2</sub>O; 0.367 g, 2.4 mmol), O-benzotriazole-N,N,N',N'-tetramethyluronium  
15 hexafluorophosphate (HBTU; 0.91 g, 2.4 mmol), and DIEA (0.55 mL, 3.2 mmol). The reaction mixture was agitated overnight at room temperature using a wrist arm shaker. The resin was isolated on a sintered glass funnel by suction filtration and washed with dimethylformamide (3  
20 X 50 mL). Unreacted amine groups were then capped by reacting the resin with 20% (v/v) acetic anhydride/dimethylformamide (2 X 25 mL) directly in the funnel (10 min/wash). The resin was washed with dimethylformamide (3 X 50 mL) and dichloromethane (3 X  
25 50 mL) prior to drying overnight *in vacuo* to yield **614** (11.0 g, quantitative yield).

**Step B. Synthesis of 616.** Resin **614** (3.0 g, 0.16 mmol/g, 0.48 mmol) was swelled in a sintered glass funnel by washing with dimethylformamide (3 X 15 mL).  
30 The Fmoc protecting group was then cleaved with 25% (v/v) piperidine/dimethylformamide (15 mL) for 10 min

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(intermittent stirring) and then for 20 min with fresh piperidine reagent (15 ml). The resin was then washed with dimethylformamide (3 X 15 ml), followed by N-methylpyrrolidone (2 X 15 mL). After transferring the resin to a 100 mL flask, N-methylpyrrolidone was added to obtain a slurry followed by **603u** (0.736 g, 0.72 mmol), HOBT·H<sub>2</sub>O (0.112 g, 0.73 mmol), HBTU (0.27 g, 0.73 mmol) and DIEA (0.26 mL, 1.5 mmol). The reaction mixture was agitated overnight at room temperature using a wrist arm shaker. The resin work-up and capping with 20% (v/v) acetic anhydride in dimethylformamide were performed as described for **614** to yield **616** (3.13 g, quantitative yield).

**Step C. Synthesis of 617.** This compound was prepared from resin **616** (0.24 g, 0.038 mmol) using an Advanced ChemTech 396 Multiple Peptide synthesizer. The automated cycles consisted of a resin wash with dimethylformamide (3 X 1 mL), deprotection with 25% (v/v) piperidine in dimethylformamide (1 mL) for 3 min followed by fresh reagent (1 mL) for 10 min to yield resin **617**. The resin was washed with dimethylformamide (3 X 1 mL) and N-methylpyrrolidone (3 X 1 mL).

**Step D. Method 1. (624).** Resin **617** was acylated with a solution of 0.4M thiophene-3-carboxylic acid and 0.4M HOBT in N-methylpyrrolidone (1 mL), a solution of 0.4M HBTU in N-methylpyrrolidone (0.5 mL) and a solution of 1.6M DIEA in N-methylpyrrolidone (0.35 mL) and the reaction was shaken for 2 hr at room temperature. The acylation step was repeated. Finally, the resin was washed with dimethylformamide (3 X 1 mL), dichloromethane (3 X 1 mL) and dried *in vacuo*.

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The aldehyde was cleaved from the resin and globally deprotected by treatment with 95% TFA/ 5% H<sub>2</sub>O (v/v, 1.5 mL) for 30 min at room temperature. After washing the resin with cleavage reagent (1 mL), the combined  
5 filtrates were added to cold 1:1 ether:pentane (12 mL) and the resulting precipitate was isolated by centrifugation and decantation. The resulting pellet was dissolved in 10% acetonitrile/90% H<sub>2</sub>O/0.1% TFA (15 mL) and lyophilized to obtain crude **624** as a white  
10 powder. The compound was purified by semi-prep RP-HPLC with a Rainin Microsorb™ C18 column (5  $\mu$ , 21.4 X 250 mm) eluting with a linear acetonitrile gradient (5% - 45%) containing 0.1% TFA (v/v) over 45 min at 12 mL/min. Fractions containing the desired product were  
15 pooled and lyophilized to provide **624** (10.0 mg, 54%).

**Step D. Method 1A. Synthesis of 627.** Following a similar procedure as method 1, resin **617** was acylated with 4-(1-fluorenylmethoxycarbonylamino)benzoic acid and repeated. The Fmoc group was removed as described  
20 in Step C and the free amine was acetylated with 20% (v/v) acetic anhydride in dimethylformamide (1 mL) and 1.6M DIEA in N-methylpyrrolidone (0.35 mL) for 2 hr at room temperature. The acetylation step was repeated. Cleavage of the aldehyde from the resin gave **627** (4.2  
25 mg, 20%).

**Step D. Method 2. Synthesis of 632.** Following a similar procedure as method 1, resin **617** was acylated with 0.5M cinnamoyl chloride in N-methylpyrrolidone (1 mL) and 1.6M DIEA in N-methylpyrrolidone (0.35 mL) for 2  
30 hr at room temperature. The acylation step was

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repeated. Cleavage of the aldehyde from the resin gave **632** (11.1 mg, 58%).

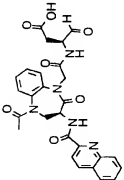
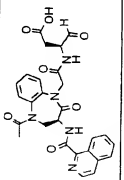
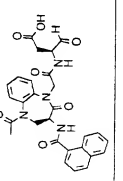
**Step D. Method 3. Synthesis of 629.** Following a similar procedure as method 1, resin **617** was reacted  
5 with 1.0M benzenesulfonyl chloride in dichloromethane (0.5 mL) and 1M pyridine in dichloromethane (0.60 mL) for 4 hr at room temperature. The reaction was repeated. Cleavage of the aldehyde from the resin **629** (4.7 mg, 24%).

10 **Analytical HPLC methods:**

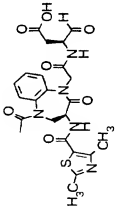
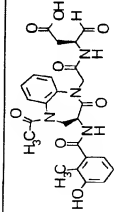
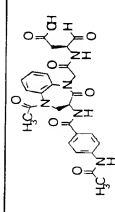
(1) Waters DeltaPak C18, 300A (5 $\mu$ , 3.9 X 150 mm).  
Linear acetonitrile gradient (5% - 45%) containing 0.1%  
TFA (v/v) over 14 min at 1 mL/min.



Table 14

| Compd. | Structure  | MF         | MW     | HPIC RT<br>min   | MS<br>(M+H) <sup>+</sup>   | Syn.<br>Method |
|--------|--|------------|--------|------------------|----------------------------|----------------|
| 619    |  | C27H25N5O7 | 531.53 | 11.71 (1)<br>98% | 532                        | 1              |
| 620    |  | C27H25N5O7 | 531.53 | 10.44 (1)<br>98% | 532                        | 1              |
| 621    |  | C28H26N4O7 | 530.54 | 11.57 (1)<br>98% | (M+Na) <sup>+</sup><br>553 | 2              |

| Compd. | Structure | MF          | MW     | HPLC RT<br>min   | MS<br>(M+H) +   | Syn.<br>Method |
|--------|-----------|-------------|--------|------------------|-----------------|----------------|
| 622    |           | C28H26N4O8  | 546.54 | 10.19 (1)<br>98% | (M+Na) +<br>569 | 1              |
| 623    |           | C39H32N4O10 | 716.71 | 15.8 (1)<br>09%  | (M-) +<br>716   | 2              |
| 624    |           | C22H22N4O7S | 486.51 | 8.39 (1)<br>98%  | 487             | 1              |

| Cmpd. | Structure  | MF          | MW     | HPLC RT<br>min  | MS<br>(M+H) <sup>+</sup> | Syn.<br>Method |
|-------|--|-------------|--------|-----------------|--------------------------|----------------|
| 625   |  | C23H25N5O7S | 515.55 | 7.60 (1)<br>98% | 516                      | 1              |
| 626   |  | C25H26N4O8  | 510.51 | 7.58 (1)<br>98% | 511                      | 1              |
| 627   |  | C26H27N5O8  | 537.53 | 7.96 (1)<br>98% | 538                      | 1A             |

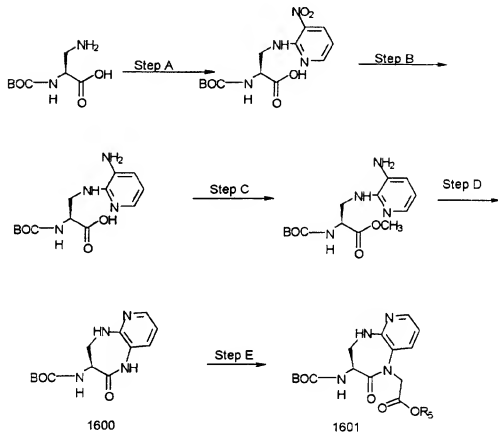
| Compd. | Structure | MF          | MW     | HPLC RT<br>min   | MS<br>(N+H) + | Syn.<br>Method |
|--------|-----------|-------------|--------|------------------|---------------|----------------|
| 628    |           | C25H24N4O9  | 524.49 | 9.50 (1)<br>98%  | 525           | 1              |
| 629    |           | C23H24N4O8S | 516.53 | 9.85 (1)<br>98%  | 517           | 3              |
| 630    |           | C25H26N4O7  | 494.51 | 9.25 (1)<br>98%  | 495           | 2              |
| 631    |           | C24H26N4O8S | 530.56 | 10.19 (1)<br>98% | 531           | 3              |

| Compd. | Structure | MF         | MW     | HPLC RT<br>min   | MS<br>(M+H) <sup>+</sup> | Syn.<br>Method |
|--------|-----------|------------|--------|------------------|--------------------------|----------------|
| 632    |           | C26H26N4O7 | 506.52 | 10.99 (1)<br>98% | 507                      | 2              |
| 633    |           | C25H26N4O8 | 510.51 | 11.48 (1)<br>98% | 511                      | 2              |
| 634    |           | C22H26N4O9 | 490.47 | 6.87 (1)<br>98%  | 491                      | 2              |
| 635    |           | C25H24N4O8 | 508.49 | 10.03 (1)<br>98% | 509                      | 1              |

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Example 14

Compounds **1605a-j**, **1605m**, **1605n**, **1605p**, **1605t**, and **1605v** were synthesized as described below.



(3*S*) *N*-(2-Oxo-3-*tert*-butoxycarbonylamino-2,3,4,5-tetrahydro-1*H*-pyrido [3,4-*b*] [1,4-diazepine (**1600**)).

**Step A.** (2*S*) 2-*tert*-Butoxycarbonylamino-3-(3-nitropyridin-2-ylamino)propionic acid was prepared by a similar method as (2*S*) 2-*tert*-butoxycarbonylamino-3-(2-nitrophenyl-amino)propionic acid in Step A of the synthesis of **600a/103**, except that 3-chloro-3-nitro pyridine was used instead of 2-

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fluoronitrobenzene, to give 4.05 g (64%) of a yellow solid.

Step B. (2S) 2-*tert*-Butoxycarbonylamino-3-(3-aminopyridin-2-ylamino)propionic acid was prepared by a similar method to (2S) 2-*tert*-Butoxycarbonylamino-3-(2-aminophenylamino)-propionic acid in Step B of the synthesis of 600a/103 to give 3.68 g (quant.) as a dark solid.

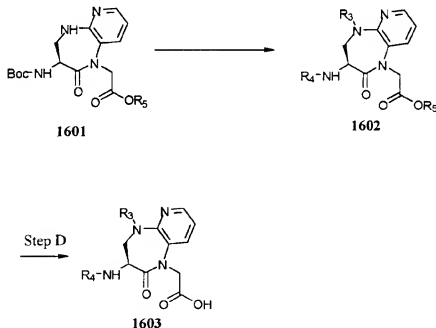
Step C. (2S) 2-*tert*-Butoxycarbonylamino-3-(3-aminopyridin-2-ylamino)propionic acid methyl ester. A solution of (2S) 2-*tert*-Butoxycarbonylamino-3-(3-aminopyridin-2-ylamino)-propionic acid (360 mg, 1.21 mmol) and MeOH (59 mg, 1.82 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (20 ml) was treated with 4-dimethylaminopyridine (DMAP, 163 mg, 1.33 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (280 mg, 1.45 mmol). The reaction was stirred for 18 h, diluted with EtOAc (150ml), washed with water (2x), sat. aq. NaHCO<sub>3</sub>, and sat. aq. NaCl, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. Chromatography (flash, SiO<sub>2</sub>, 0 to 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) gave 250 mg (67%) of the title compound as a light tan solid.

Step D. (3S) N-(2-Oxo-3-*tert*-butoxycarbonylamino-2,3,4,5-tetrahydro-1H-pyrido[3,4-b][1,4-diazepine (1600)). A solution of (2S) 2-*tert*-butoxycarbonylamino-3-(3-aminopyridin-2-ylamino)propionic acid methyl ester (70 mg, 0.225 mol) and 25% sodium methoxide/MeOH (130  $\mu$ l, 0.56 mmol) in anhydrous MeOH (4 ml) was heated at 60°C for 16 h.

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The reaction was concentrated *in vacuo*, the residue dissolved in 2 ml of H<sub>2</sub>O and extracted with EtOAc (3x). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. Chromatography (flash, SiO<sub>2</sub>, 0 to 3% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) gave 7.5 mg (3%) of **1600** as a light tan solid: <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.96-7.92 (1H, d), 7.75-7.65 (1H, br. s), 7.14-7.08 (1H, d), 6.73-6.65 (1H, m), 5.83-5.75 (1H, br. s), 5.4-5.25 (1H, br. s), 4.6-4.5 (1H, m), 3.95-3.84 (1H, m), 3.55-3.48 (1H, m), 1.4 (9H, s)

**Step E.** **1601** is prepared from **1600** following the method in Step D for the preparation **600a/103**.

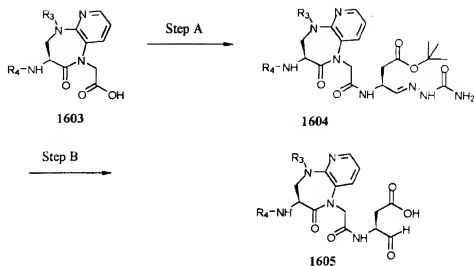


**Synthesis of 1603.** **1603** is prepared from **1601** following the methods for the synthesis of **603** from

**600.**



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**Synthesis of 1605.** 1605 is prepared from 1603 by methods described for the synthesis of 605 from 603.

**Table 15**

|    | 1605 | $R_3$                                   | $R_4$         |
|----|------|---|---------------|
| 5  | a    | $\text{PhCH}_2\text{CH}_2\text{CO}$     | $\text{PhCO}$ |
|    | b    | $\text{PhCH}_2\text{CO}$                | $\text{PhCO}$ |
|    | c    | $\text{PhCO}$                           | $\text{PhCO}$ |
|    | d    | $\text{CH}_3\text{CO}$                  | $\text{PhCO}$ |
|    | e    | $\text{CH}_3\text{OCH}_2\text{CO}$      | $\text{PhCO}$ |
| 10 | f    | $(\text{CH}_3)_2\text{CHCH}_2\text{CO}$ | $\text{PhCO}$ |
|    | g    | $\text{CH}_3\text{COCH}_2\text{CO}$     | $\text{PhCO}$ |
|    | h    | $\text{CH}_3\text{OCOCO}$               | $\text{PhCO}$ |
|    | i    | $\text{CH}_3\text{COCO}$                | $\text{PhCO}$ |
|    | j    | $\text{CH}_3\text{OCO}$                 | $\text{PhCO}$ |
| 15 | m    | $\text{CH}_3\text{SO}_3$                | $\text{PhCO}$ |
|    | n    | $\text{CH}_3\text{CO}$                  | Naphthyl-2-CO |
|    | p    | $\text{PhCH}_2\text{NHCO}$              | $\text{PhCO}$ |

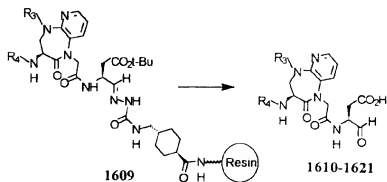
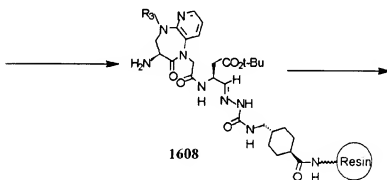
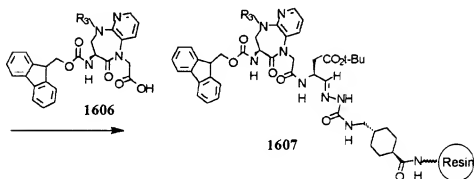
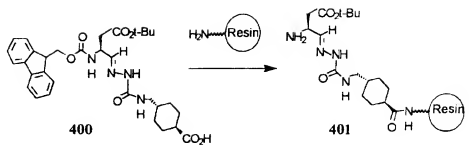
- 516 -

|   |  |                   |
|---|--|-------------------|
| t | 3-CH <sub>3</sub> PhCH <sub>2</sub> CO | PhCO              |
| v | PhCH <sub>2</sub> CH <sub>2</sub> CO   | PhCH <sub>2</sub> |

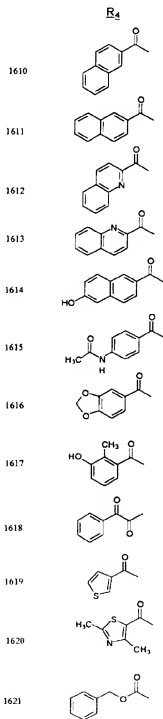
Example 15

Compounds **1610-1621** are prepared from **1600**  
5 by methods similar to the methods used to prepare  
compounds **619-635** from **600a/103** and **600b**.

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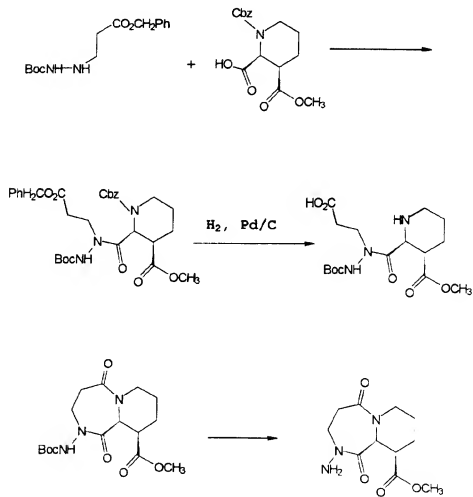
wherein for compounds **1610-1621**,a  $R_3 = \text{CH}_3\text{C(O)-}$ b  $R_3 = \text{CH}_3\text{OCH}_2\text{C(O)-}$ 

- 5.9 -

Example 16

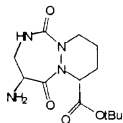
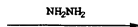
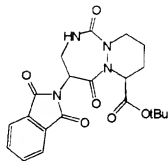
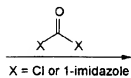
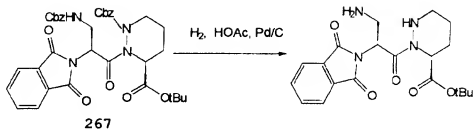
Compounds comprising scaffolds (e11), (y1), (y2), (z), and (e12) may be synthesized as described below.

- 5 Synthesis of Scaffold  $R_1$ , wherein  $R_1$  is (e11) and wherein  $Y_2$  is =O.



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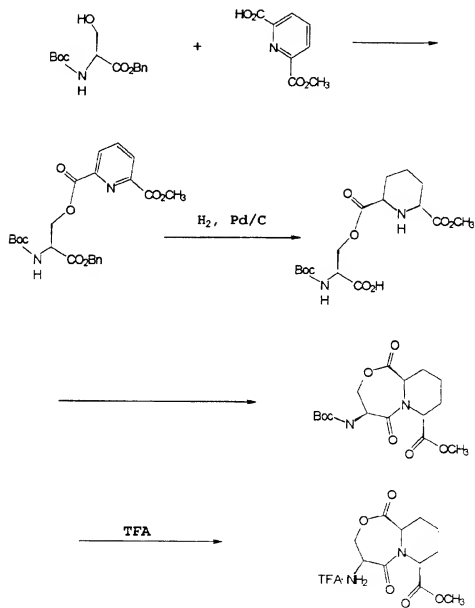
Synthesis of Scaffold  $R_1$ , wherein  $R_1$  is (y1) and wherein  $Y_2$  is =O.



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Synthesis of Scaffold  $R_1$ , wherein  $R_1$  is (y2) and wherein  $Y_2$  is  $H_2$  and  $X_7$  is O.

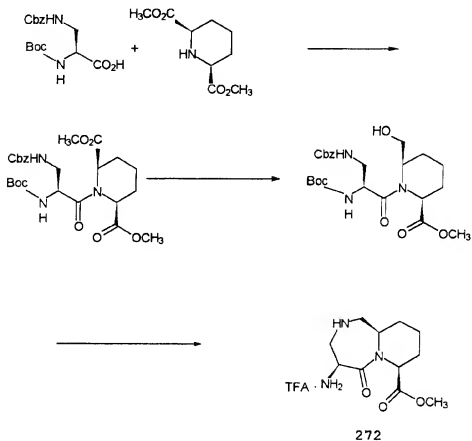






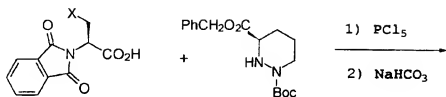
- 523 -

Synthesis of Scaffold  $R_1$ , wherein  $R_1$  is (y2) and wherein  $Y_2$  is  $H_2$  and  $X_7$  is NH.

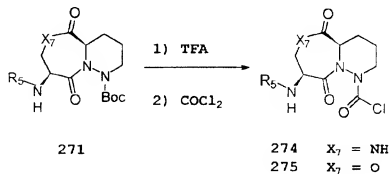
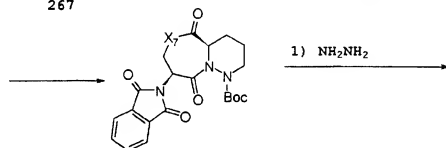
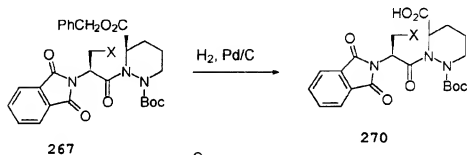


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Synthesis of Scaffold  $R_1$ , wherein  $R_1$  is (z) and wherein  $Y_2$  is O.

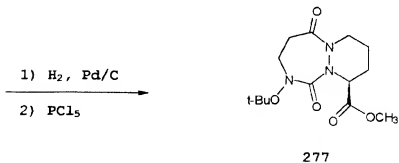
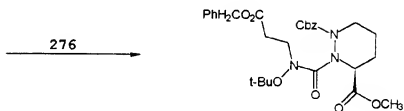
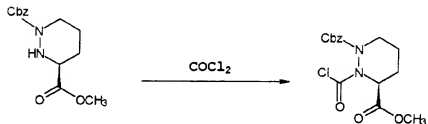
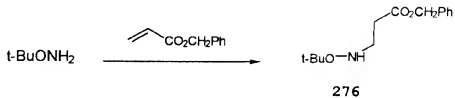


$X = \text{NHCbz}$   
 $X = \text{OCH}_2\text{Ph}$



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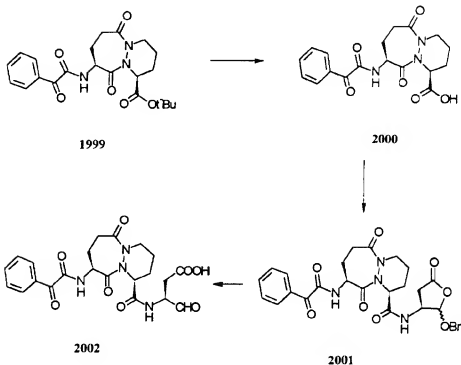
Synthesis of Scaffold  $R_1$ , wherein  $R_1$  is (e12) and wherein  $Y_2$  is =O.



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Example 17

The preparation of compounds 2001, 2002, 2100a-e, and 2201 is described below.



- (1*S*,9*S*) 9-Benzoylformylamino-6,10-dioxo-  
 5 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a]-[1,2]  
 diazepine-1-carboxylic acid (2000). To a solution of  
 t-butyl 9-amino-6,10-dioxo-1,2,3,4,7,8,9,10-  
 octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-  
 carboxylate (GB 2,128,984; 340 mg, 1.15 mmol) in  
 10 CH<sub>2</sub>Cl<sub>2</sub> was added benzoylformic acid (260 mg, 1.7  
 mmol), HOBT (230 mg, 1.7 mmol) and EDC (340 mg, 1.7  
 mmol). The resulting mixture was stirred at ambient  
 temperature for 16 hours, poured into 1N HCl and  
 extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic extracts were

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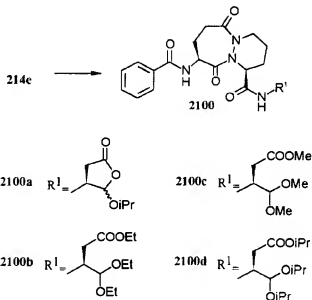
further washed with saturated  $\text{NaHCO}_3$ , dried over  $\text{MgSO}_4$  and concentrated to afford **1999** as a pale yellow solid. The solid was dissolved in  $\text{CH}_2\text{Cl}_2$  (25 ml) and TFA (25 ml) and stirred overnight and concentrated in vacuo to give 560 mg of **2000** as an oil.

[1*S*,9*S*(2*RS*,3*S*)] 9-Benzoylformylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2(*R,S*)-benzyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamide (**2001**), was synthesized from **2000** by methods similar to compound **213e** to afford 410 mg (63%) of **2001** as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ; mixture of diastereomers)  $\delta$  8.25 (1H, d), 8.23 (1H, d), 7.78 (1H, dd), 7.65 (1H, bm), 7.50 (2H, m), 7.40-7.25 (4H, m), 6.55 (1H, d), 5.57 (1H, d), 5.10 (1H, t), 5.05-4.95 (2H, m), 4.90, (1H, d), 4.80 (1H, d), 4.72 (1H, bm), 4.65 (1H, m), 4.55 (1H, m), 4.45 (1H, t), 3.25 (1H, m), 3.15 (1H, m), 3.00 (2H, bm), 2.90 (1H, dd), 2.70 (1H, m), 2.47 (1H, dd), 2.45 (1H, m), 2.35 (1H, m), 2.00-1.75 (4H, m), 1.60 (1H, bm).

[3*S*(1*S*,9*S*)] 3-(9-Benzoylformylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-4-oxobutanoic acid (**2002**). Compound **2001** (58.6 mg, 0.10 mmol) was treated with 15 ml of TFA/MeCN/water (1:2:3) and stirred at room temperature for 6.5 h. The reaction was extracted with ether. The aqueous layer was concentrated with azeotropic removal of the water using MeCN. The product was suspended in  $\text{CH}_2\text{Cl}_2$ , concentrated in vacuo and precipitated with ether to give 46.8 mg

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(99%) of **2002** as a white solid:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  9.05 (0.25H, d), 8.15 (1H, d), 7.68 (1H, t), 7.64 (0.25H, d), 7.55 (3H, t), 7.35 (0.5H, m), 5.22 (1H, t), 4.90 (1H, m), 4.58 (1H, dd), 4.50 (1H, m), 4.28 (1H, bm), 3.45 (1H, m), 3.10 (1H, bt), 2.68 (1H, ddd), 2.60-2.45 (2H, m), 2.30 (1H, dd), 2.15-2.05 (2H, m), 1.90 (2H, bm), 1.68 (1H, bm).



[1S,9S(2RS,3S)] 9-Benzoylamino-6,10-dioxo-  
1,2,3,4,7,8,9,10-octahydro-N-(2-isopropoxy-5-oxo-  
10 tetrahydro-furan-3-yl)-6H-pyridazino-  
[1,2-a][1,2]diazepine-1-carboxamide (2100a). A  
solution of 214e (101 mg, 0.23 mmol) in isopropanol  
(10 ml) was stirred at room temperature with a  
catalytic amount of *p*-toluenesulfonic acid (10 mg).  
15 After 75 minutes, the reaction mixture was poured  
into saturated NaHCO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The  
combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and

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concentrated. Flash chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub> to EtOAc) afforded 56 mg (51%) of **2100a** as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>; mixture of diastereomers) δ 7.9-7.8 (2H,m), 7.6-7.5 (1H, m), 7.5-7.4 (2H, m), 7.1 (0.5H, d), 6.9 (0.5H, d), 6.4 (0.5H,d), 5.6 (0.5H, d), 5.3 (0.5H, s), 5.2-5.1 (1H, m), 4.95 (0.5H, m), 4.75-4.5 (1.5H, m), 4.35 (0.5H, t), 4.1 (0.5H, m), 3.98 (0.5H, m), 3.3-2.75 (4H, m), 2.5-2.4 (2H,m), 2.25 (1H, m), 2.1-1.9 (3H,m) 1.75-1.55 (2H,m).

- 10 **[3S(1S,9S)] 3-(9-Benzoylformylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-4,4-diethoxy-butyric acid, ethyl ester (2100b)**. A solution of **214e** (16 mg, 0.036 mmol) in ethanol (2 ml) was stirred at room
- 15 temperature with a catalytic amount of *p*-toluenesulfonic acid (2 mg). After 5 days, the reaction mixture was poured into saturated NaHCO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. Flash
- 20 chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>:EtOAc 95:5 v/v) afforded 16 mg (81%) of **2100b** as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.85-7.74 (2H,m), 7.55-7.38 (3H,m), 7.04-6.95 (1H,d), 6.61-6.48 (1H,d), 5.15-5.08 (1H,m), 4.63-4.53 (1H,m), 4.52-4.45 (1H,m), 4.42-4.35 (1H,m),
- 25 4.15-4.05 (2H,m), 3.74-3.60 (2H,m), 3.57-3.42 (2H,m), 3.39-3.28 (1H,m), 3.03-2.93 (1H,m), 2.92-2.82 (1H,m), 2.65-2.52 (2H,m), 2.42-2.25 (1H,m), 2.20-1.88 (4H,m), 1.76-1.50 (2H,m), 1.35-1.10 (9H,m).

- [3S(1S,9S)] 3-(9-Benzoylformylamino-6,10-dioxo-**
- 30 **1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-4,4-dimethoxy-butyric acid**

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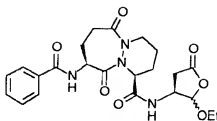
**methyl ester (2100c).** A solution of **214e** (165 mg, 0.37 mmol) in methanol (5 ml) was stirred at room temperature with a catalytic amount of *p*-toluenesulfonic acid (17.5 mg). After 4 days, the reaction mixture was diluted with EtOAc and washed with 10% NaHCO<sub>3</sub> (3x) and brine. The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. Flash chromatography (SiO<sub>2</sub>, EtOAc) afforded 127 mg (68%) of **2100c** as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.82 (2H, d), 7.55-7.50 (1H, m), 7.47-7.43 (2H, m), 7.02 (1H, d), 6.53 (1H, d), 5.20-5.10 (1H, m), 4.56-4.50 (1H, m), 4.45-4.50 (1H each, two m), 3.69 (3H, s), 3.41 (3H, s), 3.43 (3H, s), 3.35-3.25 (1H, m), 3.06-2.98 (1H, m), 2.94-2.83 (1H, m), 2.65-2.53 (2H, m), 2.35-2.32 (1H, m), 2.15-2.07 (1H, m), 2.00-1.89 (3H, m), 1.75-1.56 (2H, m).

**[3*S*(1*S*,9*S*)] 3-(9-Benzoylformylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]-diazepine-1-carboxamido)-4,4-diisopropoxy-butyric acid, isopropyl ester (2100d).** A solution of **214e** (53 mg, 0.12 mmol) in isopropanol (5 ml) was stirred at 50 °C with a catalytic amount of *p*-toluenesulfonic acid (5 mg). After 3 days the reaction mixture was poured into saturated NaHCO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. Flash chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>:EtOAc (4:1 to 1:1 v/v)) afforded 49 mg (68%) of **2100d** as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.85 (2H, d), 7.50-7.43 (1H, m), 7.41-7.35 (2H, m), 7.02 (1H, d), 6.47 (1H, d), 5.13-5.07 (1H, m), 5.00-4.9 (1H, m), 4.61-4.55 (2H, m), 4.37-4.30 (1H, m), 3.80-3.70 (1H, m), 3.90-3.80 (1H, m), 3.42-3.35 (1H, m),



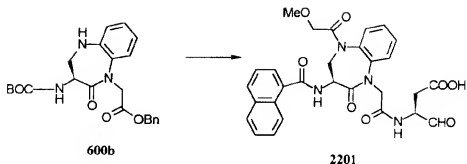
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3.03-2.93 (1H, m), 2.91-2.81 (1H, m), 2.62-2.50 (2H, m), 2.38-2.33 (1H, m), 2.12-2.06 (1H, m), 1.97-1.81 (3H, m), 1.70-1.60 (2H, m), 1.28-1.05 (18H, m).

**2100e**

- [1*S*,9*S*(2*RS*,3*S*)] 9-Benzoylamino-6,10-dioxo-  
 5 1,2,3,4,7,8,9,10-octahydro-N-(2-ethoxy-5-oxo-  
 tetrahydro-furan-3-yl)-6H-pyridazino[1,2-a][1,2]-  
 diazepine-1-carboxamide (2100e), was synthesized from  
 302 via methods used to synthesize 304a to afford  
 2100e, except ethanol and triethylorthoformate were  
 10 used instead of methanol and trimethylorthoformate.  
 Chromatography (SiO<sub>2</sub>, 5% ethanol/CH<sub>2</sub>Cl<sub>2</sub>) afforded 92  
 mg (68%) of a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>; mixture of  
 diastereomers) δ 7.90-7.80 (2H, m), 7.60-7.50 (1H,  
 m), 7.50-7.40 (2H, m), 7.30 (0.5H, d), 7.00 (0.5H,  
 d), 6.50 (0.5H, d), 5.50 (0.5H, d), 5.20-5.10 (1.5H,  
 m), 4.95 (0.5H, m), 4.75-4.65 (0.5H, m), 4.65-4.50  
 (1H, m), 4.38 (0.05H, t), 4.00-3.90 (0.5H, m), 3.85-  
 3.75 (0.5H, m), 3.75-3.65 (0.5H, m), 3.65-3.55 (0.5H,  
 m), 3.30-2.70 (4H, m), 2.50-2.35 (2H, m), 2.30 (1H,  
 15 d), 2.15-1.90 (3H, m), 1.80-1.60 (2H, m), 1.25-1.20  
 (3H, two t)

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(3*S*)-3-[(3*S*)-2-oxo-3-(1-naphthoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetylamino]4-oxo-butyrac acid

(2201) was synthesized from 600b by the methods used

5 to synthesize 605b to afford 2201:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$   
 8.30-8.22 (1*H*,m), 8.05-7.98 (1*H*, d), 7.96-7.83  
 (1*H*,m), 7.77-7.68 (1*H*,m), 7.67-7.40 (7*H*,m), 5.12-5.02  
 (1*H*,m), 4.98-4.41 (5*H*,m), 4.38-4.24 (1*H*,m), 4.07-4.00  
 (1*H*,d), 3.92-3.80 (2*H*,m), 3.32 (3*H*,s), 2.75-2.60  
 10 (1*H*,m), 2.58-2.35 (1*H*,m).

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Example 18

We obtained the following data for selected compounds of this invention using the methods described herein (Table 16, see Example 7; Tables 17 and 18, see Examples 1-4). The structures and preparations of compounds of this invention are described in Examples 28-31.

Table 16 Comparison of Prodrugs for Efficacy in LPS Challenged Mice: Inhibition of IL-1 $\beta$  Production.

The percent inhibition of IL-1 $\beta$  production after treatment with a compound of the invention is shown as a function of time after LPS challenge ("-" indicates that no value was obtained at that relative time).

|    |          | Time of Compound Administration<br>(relative to time of LPS challenge, PO, 50 mg/kg) |     |    |     |
|----|----------|--|-----|----|-----|
|    | Compound | -2h  | -1h | 0h | +1h |
|    | 213f     | (-4)   | -   | 8  | -   |
|    | 213h     | 9  | -   | 53 | -   |
|    | 213i     | (-11)  | -   | 62 | -   |
| 15 | 213k     | 0  | -   | 68 | -   |
|    | 213l     | (-18)  | -   | 80 | -   |
| 20 | 213m     | 26   | -   | 42 | -   |
|    | 213o     | 4  | -   | 8  | -   |
|    | 213p     | 21   | -   | 29 | -   |
| 25 | 213q     | 17   | -   | 91 | -   |
|    | 213r     | 59   | -   | 37 | -   |
|    | 213x     | 0  | -   | 78 | -   |
|    | 213y     | 29   | -   | 50 | -   |
|    | 214e     | 39   | -   | 70 | 75  |
|    |          | 43   | 44  | 48 | 11  |
|    |          | -  | -   | -  | 47  |
| 30 | 214k     | 12   | -   | 31 | -   |
|    | 214l     | 0  | -   | 54 | -   |
|    | 214m     | 0  | -   | 17 | -   |
|    | 214w     | 11   | -   | 91 | -   |
|    | 2641     | 0  | -   | 23 | -   |
| 35 | 404      | -  | -   | -  | 56  |
|    |          | 55   | -   | 6  | -   |

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|    | Compound | -2h   | -1h | 0h | +1h |
|----|----------|-------|-----|----|-----|
| 5  | 412      | 0     | -   | 0  | -   |
|    |          | 11    | -   | 37 | -   |
|    | 418      | -     | -   | -  | 64  |
|    |          | 25    | -   | 52 | -   |
|    | 434      | -     | -   | -  | 80  |
| 10 |          | 0     | -   | 63 | -   |
|    | 450      | 0     | -   | 35 | -   |
|    | 452      | -     | -   | -  | 70  |
|    |          | 28    | -   | 89 | -   |
|    | 456      | -     | -   | -  | 56  |
| 15 |          | 41    | -   | 69 | -   |
|    | 470      | 0     | -   | 36 | -   |
|    | 471      | 0     | -   | 34 | -   |
|    | 475      | 0     | -   | 15 | -   |
|    | 481      | 27    | -   | 0  | -   |
| 20 | 486      | 19    | -   | 15 | -   |
|    | 487      | 17    | -   | 20 | -   |
|    | 528      | 25    | -   | 67 | -   |
|    | 550f     | 0     | -   | 50 | -   |
|    | 550h     | 55    | -   | 73 | -   |
| 25 | 550i     | (-10) | -   | 23 | -   |
|    | 550k     | 36    | -   | 34 | -   |
|    | 550l     | 9     | -   | 38 | -   |
|    | 550m     | 45    | -   | 52 | -   |
|    | 550n     | 19    | -   | 65 | -   |
| 30 | 550o     | 19    | -   | 64 | -   |
|    | 550p     | 30    | -   | 60 | -   |
|    | 655      | 0     | -   | 68 | -   |
|    | 656      | 31    | -   | 16 | -   |
|    | 662      | 41    | -   | 75 | -   |
| 35 | 668      | -     | -   | -  | 53  |
|    | 695a     | 49    | -   | 78 | -   |
|    | 1015     | 15    | -   | 28 | -   |
|    | 2001     | 64    | 62  | 58 | 55  |
|    | 2001a    | 10    | -   | 16 | -   |
|    | 2002     | 5     | -   | 87 | -   |
|    | 2100h    | 34    | -   | 32 | -   |
|    | 2100i    | 19    | -   | 74 | -   |
|    | 2100j    | 48    | 41  | 0  | 33  |
|    | 2100k    | 30    | 50  | 32 | 72  |
|    | 2100l    | 52    | -   | 28 | -   |
|    | 2100m    | 40    | -   | 42 | -   |
|    | 2100n    | 21    | 9   | 64 | 73  |
|    | 2100o    | 31    | 44  | 68 | 64  |

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Table 17 Data for selected compounds of this invention obtained using the methods described in Examples 1-4.

| Compound | UV-Visible<br>Ki (nM) | Cell PBMC<br>avg. IC50<br>(nM) | Whole<br>human<br>blood<br>IC50 (nM) | Clearance<br>Mouse,<br>i.v.<br>ml/min/kg | Clearance<br>Rat, i.v.<br>ml/min/kg |
|----------|-----------------------|--------------------------------|--------------------------------------|--|-------------------------------------|
| 5 213f   |                       |                                | 3000                                 |  |                                     |
| 213g     |                       |                                | 2200                                 |  |                                     |
| 213h     |                       |                                | 1500                                 |  |                                     |
| 213i     |                       |                                | 1100                                 |  |                                     |
| 213j     |                       |                                |                                      |  |                                     |
| 213k     |                       |                                | 2000                                 |  |                                     |
| 10 213l  |                       |                                | 2000                                 |  |                                     |
| 213m     |                       |                                | 2500                                 |  |                                     |
| 213o     |                       | 5000                           | 3300                                 |  |                                     |
| 213p     |                       |                                | <300                                 |  |                                     |
| 213q     |                       |                                | <300                                 |  |                                     |
| 15 213r  |                       |                                | <300                                 |  |                                     |
| 213v     | 0.5                   | 1,100                          | 1100                                 | 41                                       | 23                                  |
| 213x     |                       | 4500                           | 2500                                 |  |                                     |
| 213y     |                       |                                | 930                                  |  |                                     |
| 214j     | 4.2                   | 2500                           | 6000                                 |  |                                     |
| 20 214k  | 0.2                   | 500                            | 580                                  |  | 22                                  |
| 214l     | 6                     | 1900                           | 1100                                 |  | 12                                  |
| 214m     | 1.5                   | 530                            | 2200                                 |  | 33.4                                |
| 214w     | 0.6                   | 620                            | 370                                  |  | 15                                  |
| 246b     | 30000                 | >30000                         |                                      | 87                                       |                                     |
| 25 264l  |                       |                                | 3000                                 |  |                                     |
| 265a     | 2600                  | 25000                          |                                      |  |                                     |
| 265c     | 1100                  | 4500                           |                                      |  | 32                                  |
| 265d     | 500                   | 1500                           |                                      |  | 35                                  |
| 265f     | 1200                  |                                |                                      |  | 24                                  |
| 30 280b  |                       | 13000                          |                                      |  |                                     |
| 280c     |                       | 10000                          |                                      |  | 86                                  |
| 280d     |                       | 25000                          |                                      |  |                                     |
| 283b     |                       | 1750                           |                                      |  | 41                                  |
| 283c     |                       | 4000                           |                                      |  | 50                                  |

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|    | Compound | UV-Visible<br>Ki (nM) | Cell PBMC<br>avg. IC50<br>(nM) | Whole<br>human<br>blood<br>IC50 (nM) | Clearance<br>Mouse,<br>i.v.<br>ml/min/kg | Clearance<br>Rat, i.v.<br>ml/min/kg |
|----|----------|-----------------------|--------------------------------|--------------------------------------|--|-------------------------------------|
|    | 283d     |                       | >8000                          | 10000                                |  |                                     |
|    | 308c     | 3000                  |                                |                                      |  |                                     |
|    | 308d     | 3000                  |                                |                                      |  |                                     |
|    | 500      | 25                    | 1800                           | 1800                                 |  |                                     |
| 5  | 501      | 2.5                   | 1800                           | 1600                                 |  |                                     |
|    | 505c     |                       | 1500                           |                                      |  |                                     |
|    | 505d     |                       | >20000                         |                                      |  |                                     |
|    | 505f     |                       | 550                            |                                      |  |                                     |
|    | 510a     | 65                    | 200                            |                                      | 267                                      |                                     |
| 10 | 510d     | 2300                  | >20000                         |                                      |  |                                     |
|    | 511c     | 730                   | >20000                         |                                      | 78                                       | 40                                  |
|    | 528      |                       |                                | 2200                                 |  |                                     |
|    | 550f     |                       |                                | 1100                                 |  |                                     |
|    | 550h     |                       |                                | 1800                                 |  |                                     |
| 15 | 550i     |                       |                                | 1400                                 |  |                                     |
|    | 550k     |                       |                                | 3000                                 |  |                                     |
|    | 550l     |                       |                                | 750                                  |  |                                     |
|    | 550m     |                       |                                | 2000                                 |  |                                     |
|    | 550n     |                       |                                | <300                                 |  |                                     |
| 20 | 550o     |                       | 450                            | 3000                                 |  |                                     |
|    | 550p     |                       |                                | 2900                                 |  |                                     |
|    | 550q     |                       |                                | 700                                  |  |                                     |
|    | 640      | 155                   | 2250                           | 3900                                 |  |                                     |
|    | 642      | 35                    | 8000                           | 2900                                 |  |                                     |
| 25 | 645      | 150                   |                                |                                      |  |                                     |
|    | 650      | 550                   | 4000                           |                                      |  |                                     |
|    | 653      | 30                    | 2300                           | 6000                                 |  |                                     |
|    | 655      |                       |                                |                                      |  |                                     |
|    | 656      | 0.6                   | 2100                           | 1600                                 |  | 2.9                                 |
| 30 | 662      | 0.5                   | 1800                           | 800                                  |  | 2.75                                |
|    | 668      | 9                     | 5200                           | 3700                                 |  | 29                                  |
|    | 669      | 14                    |                                | 10000                                |  |                                     |
|    | 670      |                       |                                | 4500                                 |  |                                     |
|    | 671      | 5                     | 2000                           | 2500                                 |  | 33.2                                |
| 35 | 677      |                       |                                | 610                                  |  |                                     |
|    | 678      | 5                     | 2700                           | 2200                                 |  |                                     |
|    | 680      |                       |                                |                                      |  |                                     |

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| Compound | UV-Visible<br>Ki (nM) | Cell PBMC<br>avg. IC50<br>(nM) | Whole<br>human<br>blood<br>IC50 (nM) | Clearance<br>Mouse,<br>i.v.,<br>ml/min/kg | Clearance<br>Rat, i.v.,<br>ml/min/kg |
|----------|-----------------------|--------------------------------|--------------------------------------|---|--------------------------------------|
| 681      | 9                     | 3000                           | 5000                                 |   |                                      |
| 682      |                       |                                | 1300                                 |   |                                      |
| 683      | 400                   | >20000                         | >20000                               |   |                                      |
| 684      | 15                    | 5000                           | 2800                                 |   |                                      |
| 5 686    | 4                     | 4000                           | 9000                                 |   |                                      |
| 688a     |                       |                                | 3000                                 |   |                                      |
| 688b     |                       |                                | 1300                                 |   |                                      |
| 689a     | 0.8                   | 910                            | 2500                                 |   |                                      |
| 689b     | 2.2                   | 600                            | 2000                                 |   |                                      |
| 10 690a  |                       |                                | 1600                                 |   |                                      |
| 690b     |                       |                                |                                      |   |                                      |
| 691a     | 2.1                   | 2900                           | 1200                                 |   | 9.9                                  |
| 691b     | 11.5                  | 1,900                          | 1400                                 |   |                                      |
| 692a     |                       |                                |                                      |   |                                      |
| 15 692b  |                       |                                | 1800                                 |   |                                      |
| 693      |                       |                                |                                      |   |                                      |
| 694      | 3                     | 2600                           | 2100                                 |   |                                      |
| 695a     |                       |                                |                                      |   |                                      |
| 695b     |                       |                                |                                      |   |                                      |
| 20 695c  |                       |                                | 2500                                 |   |                                      |
| 696      | 4.5                   | 2000                           | 2900                                 |   | 13                                   |
| 700      | 275                   |                                |                                      |   |                                      |
| 701      | 90                    |                                |                                      |   |                                      |
| 702      | 45                    | >5000                          | 20000                                |   |                                      |
| 25 703   | 5                     | 1400                           | 20000                                |   |                                      |
| 704      | 30                    | 2600                           | 9800                                 |   |                                      |
| 705      | 5                     | 2300                           | 3200                                 |   |                                      |
| 706      | 5                     | 2400                           | 5800                                 |   |                                      |
| 707      | 180                   |                                |                                      |   |                                      |
| 30 708   | 140                   |                                |                                      |   |                                      |
| 709      | 10                    | 2100                           | 14000                                |   |                                      |
| 710      | 110                   |                                |                                      |   |                                      |
| 711      | 175                   |                                |                                      |   |                                      |
| 910      | 10                    | 3400                           | 3800                                 |   |                                      |
| 35 911   | 9                     | 3500                           | 1900                                 |   |                                      |
| 912      | 10                    | 4200                           | 3800                                 |   |                                      |
| 913      | 4.5                   | 2400                           | 7000                                 |   |                                      |

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|    | Compound | UV-Visible<br>Ki (nM) | Cell PBMC<br>avg. IC50<br>(nM) | Whole<br>human<br>blood<br>IC50 (nM) | Clearance<br>Mouse,<br>i.v.<br>ml/min/kg | Clearance<br>Rat, i.v.<br>ml/min/kg |
|----|----------|-----------------------|--------------------------------|--------------------------------------|--|-------------------------------------|
|    | 914      | 5.2                   | 2600                           | 2800                                 |  |                                     |
|    | 915      | 11.5                  | >8000                          | 1900                                 |  |                                     |
|    | 918      | 7                     |                                | 1150                                 |  |                                     |
|    | 919      | 4                     | 2000                           | 4300                                 |  |                                     |
| 5  | 920      | 16                    | 2100                           | 3000                                 |  |                                     |
|    | 921      | 8.5                   | 1800                           | 3000                                 |  |                                     |
|    | 1018     | 170                   | 4000                           | 5500                                 |  | 9.1                                 |
|    | 1052     | 100                   | 2500                           |                                      |  | 16                                  |
|    | 1053     | 27                    | 2000                           | >20000                               |  | 34                                  |
| 10 | 1056     | 170                   |                                |                                      |  | 17                                  |
|    | 1075     | 120                   | 5000                           | 5500                                 |  | 14.5                                |
|    | 1095     | 360                   | 6000                           |                                      |  | 28                                  |
|    | 1105     | 250                   | 3500                           | 3000                                 |  |                                     |
|    | 1106     | 75                    | 4000                           | 1700                                 |  |                                     |
| 15 | 1107     | 65                    |                                |                                      |  |                                     |
|    | 1108     | 22                    | 1400                           | 2600                                 |  |                                     |
|    | 1109     | 80                    |                                |                                      |  |                                     |
|    | 1110     | 45                    |                                |                                      |  |                                     |
|    | 1111     | 18                    | 6050                           | 4400                                 |  |                                     |
| 20 | 1112     | 3.5                   | 1800                           | 2300                                 |  |                                     |
|    | 1113     | 290                   |                                |                                      |  |                                     |
|    | 1114     | 125                   |                                |                                      |  |                                     |
|    | 1115     | 250                   |                                |                                      |  |                                     |
|    | 1116     | 215                   |                                |                                      |  |                                     |
| 25 | 1117     | 35                    | 1700                           | 1300                                 |  |                                     |
|    | 1118     | 380                   |                                |                                      |  |                                     |
|    | 1119     | 515                   |                                |                                      |  |                                     |
|    | 1120     | 95                    |                                |                                      |  |                                     |
|    | 1121     | 170                   |                                |                                      |  |                                     |
| 30 | 1122     | 400                   |                                |                                      |  |                                     |
|    | 1123     | 30                    | 2,400                          | 4500                                 |  |                                     |
|    | 1124     | 270                   |                                |                                      |  |                                     |
|    | 1125     | 55                    | 2300                           | 9000                                 |  |                                     |
|    | 2001a    |                       |                                | 3000                                 |  |                                     |
| 35 | 2100f    |                       |                                |                                      |  |                                     |
|    | 2100g    |                       |                                |                                      |  |                                     |
|    | 2100h    |                       |                                | 2000                                 |  |                                     |



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| Compound | UV-Visible<br>Ki (nM) | Cell PBMC<br>avg. IC50<br>(nM) | Whole<br>human<br>blood<br>IC50 (nM) | Clearance<br>Mouse,<br>i.v.,<br>ml/min/kg | Clearance<br>Rat, i.v.,<br>ml/min/kg |
|----------|-----------------------|--------------------------------|--------------------------------------|---|--------------------------------------|
| 2100i    |                       |                                |                                      |   |                                      |
| 2100j    | 30000                 |                                | 12000                                |   |                                      |
| 2100k    | 520                   | 4000                           | 600                                  |   |                                      |
| 2100l    |                       | 750                            | 2200                                 |   |                                      |
| 2100m    |                       |                                |                                      |   |                                      |
| 2100n    | 670                   | 770                            | 4000                                 |   |                                      |
| 2100o    | 670                   | 1150                           | 1500                                 |   |                                      |

We obtained the following data for selected compounds of this invention (Table 18) using the methods described herein (see Examples 1-4). The structures and preparations of compounds of this invention are described in Examples 28-31.

Table 18

| Cmpd. | Fluorescent<br>Assay<br>kinact<br>m <sup>-1</sup> s <sup>-1</sup> | Cell PBMC<br>avg. IC50<br>(nM) | Whole<br>human<br>blood<br>IC50<br>(nM) | Clearance<br>Mouse,<br>i.v.,<br>ml/min/kg | Clearance<br>Rat,<br>i.v.,<br>ml/min/kg |
|-------|---|--------------------------------|---|---|---|
| 286   | 370000  | 300                            | 1600                                    |   | 119                                     |
| 505 b | 190000  | 1500                           | 2100                                    | 161                                       | 196                                     |
| 505 e | 420000  | 9000                           | 1000                                    |   |   |

Example 19

In vivo acute assay for efficacy as  
anti-inflammatory agent

Results in the Table 19 show that 412f, 412d and 696a inhibit IL-1 $\beta$  production in LPS-challenged mice after oral administration using ethanol/PEG/water,

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$\beta$ -cyclodextrin, labrosol/water or cremophor/water as vehicles. The compound was dosed at time of LPS challenge. The protocol is described in Example 7.

5 Table 19 Inhibition (%) of IL-1 $\beta$  production in LPS-challenged mice.

| Compound | 10 mg/kg<br>dose | 25 mg/kg<br>dose | 50 mg/kg<br>dose |
|----------|------------------|------------------|------------------|
| 412f     | 17%              | 25%              | 32%              |
| 412e     | 5%               | 17%              | 61%              |
| 696a     | 0                | 45%              | 52%              |

10

Example 20Mouse Carrageenan Peritoneal Inflammation

Inflammation was induced in mice with an intraperitoneal (IP) injection of 10 mg carrageenan in 0.5 ml of saline (Griswold et al., Inflammation, 13, 15 pp. 727-739 (1989)). Drugs are administered by oral gavage in ethanol/PEG/water,  $\beta$ -cyclodextrin, labrosol/water or cremophor/water vehicle. The mice are sacrificed at 4 hours post carrageenan administration, then injected IP with 2 ml of saline containing 5U/ml 20 heparin. After gentle massage of the peritoneum, a small incision is made, the contents collected and volume recorded. Samples are kept on ice until centrifuged (130 x g, 8 mins at 4 °C) to remove cellular material, and the resultant supernatant stored 25 at -20 °C. IL-1 $\beta$  levels in the peritoneal fluid are determined by ELISA.

Results in the Table 20 show prodrug 412f inhibits IL-1 $\beta$  production in carrageenan-challenged mice after oral administration of drug. Compound 214e

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did not inhibit IL-1 $\beta$  production when dosed orally at 50 mg/kg.

Table 20 Inhibition (%) of IL-1 $\beta$  production by 412f and 412d in carrageenan-challenged mice.

|    |  |                 |               |               |
|----|--|-----------------|---------------|---------------|
| 5  |  | Dose<br>(mg/kg) | Compound 412f | Compound 412d |
|    |  | 1               | 30%           | 0             |
|    |  | 10              | 54%           | 32%           |
|    |  | 25              | 49%           | 31%           |
| 10 |  | 50              | 73%           | 36%           |
|    |  | 100             | 75%           | 53%           |

#### Example 21

##### Type II Collagen-induced Arthritis

- 15           Type II collagen-induced arthritis was established in male DBA/1J mice at described Wooley and Geiger (Wooley, P.H., Methods in Enzymology, 162, pp. 361-373 (1988) and Geiger, T., Clinical and Experimental Rheumatology, 11, pp. 515-522 (1993)).
- 20   Chick sternum Type II collagen (4 mg/kg in 10 mM acetic acid) was emulsified with an equal volume of Freund's complete adjuvant (FCA) by repeated passages (400) between two 10 ml glass syringes with a gauge 16 double-hub needle. Mice were immunized by intradermal
- 25   injection (50  $\mu$ l; 100 $\mu$ l CII per mouse) of collagen emulsion 21 days later at the contra-lateral side of the tail base. Drugs were administered twice a day (10, 25 and 50 mg/kg) by oral gavage approximately 7 h apart. Vehicles used included ethanol/PEG/water,  $\beta$ -
- 30   cyclodextrin, labrosol/water or cremophor/water. Drug treatments were initiated within 2 h of the CII booster

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immunization. Inflammation was scored on a 1 to 4 scale of increasing severity on the two front paws and the scores are added to give the final score.

Results in the Figs. 12, 13 and 14 show  
5 prodrugs **412f**, **412d** and **696a** inhibit inflammation in collagen-induced arthritis in mice after oral administration. Compound **214e** did not inhibit inflammation when dosed (50 mg/kg) once a day by oral gavage.

10

#### Example 22

##### In vivo bioavailability determination

The drugs (10-100 mg/kg) were dosed orally to rats (10 mL/kg) in ethanol/PEG/water,  $\beta$ -cyclodextrin, labrosol/water or cremophor/water. Blood samples were  
15 drawn from the carotid artery at 0.25, 0.50, 1, 1.5, 2, 3, 4, 6, and 8 hours after dosing, centrifuged to plasma and stored at -70°C until analysis. Aldehyde concentrations were determined using an enzymatic assay. Pharmacokinetic analysis of data was performed  
20 by non-linear regression using RStrip (MicroMath Software, UT). Drug availability values were determined as follows:  $(\text{AUC of drug after oral prodrug dosing} / \text{AUC of drug after i.v. dosing of drug}) \times (\text{dose i.v.} / \text{dose p.o.}) \times 100\%$ .

25

Results in Table 21 show that prodrugs **412f**, **412d** and **696a** give significant blood levels of drug and have good drug availability when dosed orally. Blood levels of **214e** were not detected when it was dosed orally.

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Table 21 Oral Bioavailability of 412f, 412d, 696a and 214e in Rat.

| Compound | Dose (mg/kg) | Cmax (μg/ml) | Drug Availability (%) |
|----------|--------------|--------------|-----------------------|
| 412f     | 25           | 2.4          | 32                    |
| 412d     | 25           | 2.6          | 35                    |
| 696a     | 50           | 1.2          | 10                    |
| 214e     | 45           | 0.2          | 0.9%                  |

### Example 23

#### ICE cleaves and activates pro-IGIF

##### 10 ICE and ICE homolog expression plasmids

A 0.6 kb cDNA encoding full length murine pro-IGIF (H. Okamura et al., *Nature*, 378, p. 88 (1995)) was ligated into the mammalian expression vector pCDLSRα (Y. Takebe et al., *Mol. Cell Biol.*, 8, p. 466 (1988)).

Generally, plasmids (3 μg) encoding active ICE (above), or the three ICE-related enzymes TX, CPP32, and CMH-1 in the pCDLSRα expression vector (C. Faucheu et al., *EMBO*, 14, p. 1914 (1995); Y. Gu et al., *EMBO*, 14, p. 1923 (1995); J. A. Lippke et al., *J. Biol. Chem.*, 271, p. 1825 (1996)), were transfected into subconfluent monolayers of Cos cells in 35-mm dishes using the DEAE-dextran method (Y. Gu et al., *EMBO J.*, 14, p. 1923 (1995)). Twenty-four hours later, cells were lysed and the lysates subjected to SDS-PAGE and immunoblotting using an antiserum specific for IGIF (H. Okamura et al., *Nature*, 378, p. 88 (1995)).

Polymerase chain reaction was used to introduce Nde I sites at the 5' and 3' ends of the murine pro-IGIF cDNA using the following primers: GGAATTCATATGGCTGCCATGTCAGAAGAC (forward) and GGTTAACCATATGCTAACTTTGATGTAAGTTAGTGAG (reverse). The

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resulting NdeI fragment was ligated into E. coli expression vector pET-15B(Novagen) at the NdeI site to create a plasmid that directs the synthesis of a polypeptide of 213 amino acids consisting of a 21-residue peptide (MGSSHHHHHSSGLVPRGSHM, where LVPRGS represents a thrombin cleavage site) fused in-frame to the N-terminus of pro-IGIF at Ala2, as confirmed by DNA sequencing of the plasmid and by N-terminal sequencing of the expressed proteins. E. coli strain BL21(DE3) carrying the plasmid was induced with 0.8 mM isopropyl-1-thio- $\beta$ -D-galactopyranoside for 1.5 hours at 37°C, harvested, and lysed by microfluidization (Microfluidic, Watertown, MA) in Buffer A (20 mM sodium phosphate, pH 7.0, 300 mM NaCl, 2 mM dithiothreitol, 10% glycerol, 1 mM phenylmethylsulfonyl fluoride, and 2.5  $\mu$ g/ml leupeptin). Lysates were cleared by centrifugation at 100,000 x g for 30 min. (His)6-tagged pro-IGIF protein was then purified from the supernatant by Ni-NTA-agarose (Qiagen) chromatography under conditions recommended by the manufacturer.

#### In Vitro pro-IGIF Cleavage Reactions

In vitro cleavage reactions (30  $\mu$ l) contained 2  $\mu$ g of purified pro-IGIF and various concentrations of the purified proteases in a buffer containing 20 mM Hepes, pH 7.2, 0.1% Triton X-100, 2 mM DTT, 1 mM PMSF and 2.5  $\mu$ g/ml leupeptin and were incubated for 1 hour at 37°C. Conditions for cleavage by granzyme B were as described previously (Y. Gu et al., J. Biol. Chem., 271, p. 10816 (1996)). Cleavage products were analyzed by SDS-PAGE on 16% gels and Coomassie Blue staining, and were subjected to N-terminal amino acid sequencing

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using an ABI automated peptide sequencer under conditions recommended by the manufacturer.

#### Kinetic Parameters of IGIF Cleavage by ICE

- The kinetic parameters ( $k_{cat}/K_M$ ,  $K_M$ , and  $k_{cat}$ ) for IGIF cleavage by ICE were determined as follows.
- 5  $^{35}$ S-methionine-labeled pro-IGIF (3000 cpm, prepared by *in vitro* transcription and translation using, the TNT T7-coupled reticulocyte lysate system (Promega) and pro-IGIF cDNA in a pSP73 vector as template) were
- 10 incubated in reaction mixtures of 60  $\mu$ l containing 0.1 to 1 nM recombinant ICE and 190 nM to 12  $\mu$ M of unlabeled pro-IGIF for 8-10 min at 37°C. Cleavage product concentrations were determined by SDS-PAGE and PhosphorImager analyses. The kinetic parameters were
- 15 calculated by nonlinear regression fitting of the rate vs. concentration data to the Michaelis-Menten equation using the program Enzfitter (Biosoft).

#### IFN- $\gamma$ Induction Assays

- A.E7 Th1 cells (H. Quill and R. H. Schwartz, *J. Immunol.*, 138, p. 3704 (1987)) ( $1.3 \times 10^5$  cells in 0.15 ml Click's medium supplemented with 10% FBS, 50  $\mu$ M 2-mercaptoethanol and 50 units/ml IL-2) in 96-well plates were treated with IGIF for 18-20 hours and the culture supernatant were assayed for IFN- $\gamma$  by ELISA
- 25 (Endogen, Cambridge, MA).

#### Example 24

##### Processing of pro-IGIF by ICE in Cos Cells

- Cos cells were transfected with various expression plasmid combinations as described in Example
- 30 23. Transfected Cos cells ( $3.5 \times 10^5$  cells in a 35-mm dish) were labeled for 7 hours with 1 ml of methionine-

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free DMEM containing 2.5% normal DMEM, 1% dialyzed fetal bovine serum and 300  $\mu$ Ci/ml  $^{35}$ S-methionine ( $^{35}$ S-Express Protein Labeling-Mix, New England Nuclear). Cell lysates (prepared in 20 mM Hepes, pH 7.2, 150 mM NaCl, 0.1% Triton X-100, 5 mM N-ethylmaleimide, 1 mM PMSF, 2.5  $\mu$ g/ml leupeptine) or conditioned medium were immunoprecipitated with an antiIGIF antibody that recognizes both the precursor and the mature forms of IGIF (H. Okamura et al., *Nature*, 378, p. 88 (1995)). Immunoprecipitated proteins were analyzed by SDS-PAGE (polyacrylamide gel electrophoresis) and fluorography (Fig. 2A).

We also measured the presence of IFN- $\gamma$  inducing activity in the cell lysates and the conditioned media of transfected cells (Fig. 2B). Transfected Cos cells ( $3.5 \times 10^5$  cells in a 35-mm dish) were grown in 1 ml medium for 18 hours. Media was harvested and used at 1:10 final dilution in the IFN- $\gamma$  induction assay (Example 23). Cos cell pellets from the same transfection were lysed in 100  $\mu$ l of 20 mM Hepes, pH 7.0, by freeze-thawing 3 times. Lysates were cleared by centrifugation as described above and were used at a 1:10 dilution in the assay.

#### Example 25

##### IGIF is a physiological substrate of ICE

Wild type (ICE+/+) and ICE-/- mice were primed with heat-inactivated *P. acnes*, and Kupffer cells were isolated from these mice 7 days after priming and were then challenged with 1  $\mu$ g/ml LPS for 3 hours. The amounts of IGIF in the conditioned media were measured by ELISA.



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Wild type or ICE-deficient mice were injected intraperitoneally with heat-killed *p. agnes* as described (H. Okamura et al., Infection and Immunity, 63, p. 3966 (1995)). Kupffer cells were prepared seven  
5 days later according to Tsutsui et al. (H. Tsutsui et al., Hepato-Gastroenterol., 39, p. 553 (1992)) except a nycodenz gradient was used instead of metrizamide. For each experiment, Kupffer cells from 2-3 animals were pooled and cultured in RPMI 1640 supplemented with 10%  
10 fetal calf serum and 1 µg/ml LPS. Cell lysates and conditioned medium were prepared 3 hours later.

Kupffer cells from wild type and ICE-/- mice were metabolically labeled with <sup>35</sup>S-methionine as for Cos cells (described above in Example 24) except that  
15 methionine-free RPMI 1640 was used in place of DMEM. IGIF immunoprecipitation experiments were performed on cell lysates and conditioned media and immunoprecipitates were analyzed by SDS-PAGE and fluorography as described in Example 23. See **Fig. 3**.

20

#### Example 26

##### Induction of IFN-γ Production In Vivo

LPS mixed with 0.5% carboxymethyl cellulose in PBS, pH 7.4, was administered to mice by intraperitoneal injection (30 mg/kg LPS) in a dose  
25 volume of 10 ml/kg. Blood was collected every 3 h for 24 h from groups of three ICE-deficient or wild type mice. Serum IFN-γ levels were determined by ELISA (Endogen).

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Example 27IGIF and IFN- $\gamma$  Inhibition Assays

Inhibition of IGIF processing by ICE inhibitors was measured in ICE inhibition assays as described herein (see Example 1 and Table 22).

Human PBMC Assays

Human buffy coat cells were obtained from blood donors and peripheral blood mononuclear cells (PBMC) were isolated by centrifugation in LeukoPrep tubes (Becton-Dickinson, Lincoln Park, NJ). PBMC were added ( $3 \times 10^6$ /well) to 24 well Corning tissue culture plates and after 1 hr incubation at 37°C, non-adherent cells were removed by gently washing. Adherent mononuclear cells were stimulated with LPS (1 ug/ml) with or without ICE inhibitor in 2 ml RPMI-1640-10% FBS. After 16-18 hr incubation at 37°C, IGIF and IFN- $\gamma$  were quantitated in culture supernatants by ELISA.

For example, we obtained the following data for compound 412 of this invention using the methods described herein. The structure of compound 412 is shown below.

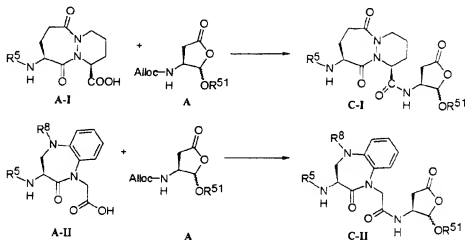
Table 22

| compound | UV-Visible<br>$K_i$ (nM) | Cell PBMC<br>avg. IC50 (nM) |
|----------|--------------------------|-----------------------------|
| 412      | 1.3                      | 580                         |

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Example 28

Compounds of this invention may be prepared via various methods. The following illustrates a preferred method:



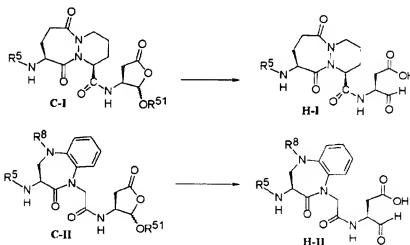
- 5 To a solution of A (1.1 equivalent) in CH<sub>2</sub>Cl<sub>2</sub> (or DMF, or CH<sub>2</sub>Cl<sub>2</sub>:DMF (1:1)) is added triphenylphosphine (0-0.5 equivalent), a nucleophilic scavenger (2-50 equivalents) and tetrakis-
- 10 triphenylphosphine palladium(0) (0.05-0.1 equivalent) at ambient temperature under inert atmosphere (nitrogen or argon). After 10 minutes, the above reaction mixture is optionally concentrated, then a solution of acid A-I or A-II in CH<sub>2</sub>Cl<sub>2</sub> (or DMF, or CH<sub>2</sub>Cl<sub>2</sub>:DMF (1:1)) is added followed by addition of HOBT (1.1 equivalent)
- 15 and EDC (1.1 equivalent). The resulting reaction mixture is allowed to stir at ambient temperature 1 hour-48 hours to provide coupled products C-I or C-II.

Various nucleophilic scavengers may be used in the above process. Merzouk and Guibe, Tetrahedron Letters, 33, pp. 477-480 (1992); Guibe and Balavoine, Journal of Organic Chemistry, 52, pp. 4984-4993

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(1987)). Preferred nucleophilic scavengers that may be used include: dimedone, morpholine, trimethylsilyl dimethylamine and dimethyl barbituric acid. More preferred nucleophilic scavengers are trimethylsilyl dimethylamine (2-5 equivalents) and dimethyl barbituric (5-50 equivalents). When the nucleophilic scavenger is trimethylsilyl dimethylamine, the above reaction mixture must be concentrated prior to addition of A-I or A-II.

10 Other compounds of this invention may be prepared by hydrolyzing compounds represented by C-I and C-II to compounds represented by H-I and H-II as described in the following scheme:



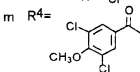
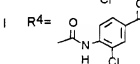
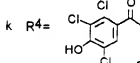
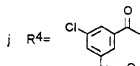
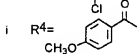
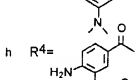
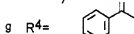
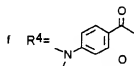
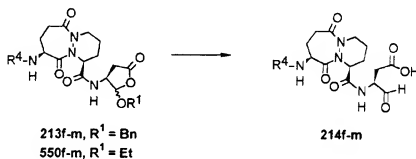
The hydrolysis may be carried out under various conditions, provided that the conditions include an acid and H<sub>2</sub>O. Acids that may be used include p-toluenesulfonic, methanesulfonic acid, sulfuric, perchloric, trifluoroacetic, and hydrochloric. For example, trifluoroacetic acid (1-90% by weight) or

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hydrochloric acid (0.1-30% by weight) in  $\text{CH}_3\text{CN}/\text{H}_2\text{O}$  (1-90%  $\text{H}_2\text{O}$  by weight) at between 0-50 °C may be used.

Example 29

Compounds **213f**, **213g**, **213h**, **213i**, **213j**, **213k**,  
 5 **213l**, **213m**, **214f**, **214g**, **214h**, **214i**, **214j**, **214k**, **214l**,  
**214m**, **550f**, **550g**, **550h**, **550i**, **550j**, **550k**, **550l** and **550m**  
 were prepared as follows.



[1*S*, 9*S* (2*RS*, 3*S*)] 9-[ (4-Dimethylaminobenzoyl) amino]-6,10-  
 dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-Benzyloxy-5-  
 10 oxotetrahydrofuran-3-yl)-6H-  
 pyridazino[1,2-a][1,2]diazepine-1-carboxamide (**213f**),  
 was synthesized from **212f** by the methods used to

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prepare **213e** from **212e** to afford 504 mg of **213f** as a yellow solid, <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 1.10(br. m, 0.25H), 1.30(br. m, 2H), 1.50(br. m, 1H), 1.65(br. m, 1.5H), 1.80(br. m, 0.25H), 1.90(br. m, 0.25H), 1.95(br. m, 0.5H), 2.05(br. m, 0.25H), 2.15(m, 1H), 2.3(m, 1H), 2.5(br. m, 1H), 2.6(dd, 1H), 2.8(m, 1H), 3.1(br. s, 3H), 3.15(br. m, 1H), 3.32(br. s, 3H), 3.5(m, 1H), 4.5(br. m, 1H), 4.62(d, 0.25H), 4.72(m, 3H), 4.95(m, 1H), 5.1(br. t, 0.25H), 5.15(br. t, 0.75H), 5.7(d, 1H), 6.75(d, 2H), 7.35(br. s, 5H), 7.75(d, 2H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3-Dimethylaminobenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (**213g**),  
was synthesized from **212g** by the methods used to prepare **213e** from **212e** to afford 400 mg of **213g**, <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 1.5(br. m, 1H), 1.65(br. m, 2H), 1.70(br. m, 0.25H), 1.90(br. m, 1H), 1.95(br. m, 1H), 2.05(br. m, 0.25H), 2.10(m, 1H), 2.3(m, 1H), 2.5(m, 2H), 2.59(d, 1H), 2.6(d, 1H), 2.78(d, 1H), 2.8(d, 1H), 2.93(br. s, 4H), 3.05(br. m, 1H), 3.15(br. m, 0.25H), 3.3(br. s, 3H), 3.5(m, 2H), 4.5(br. m, 2H), 4.65(d, 1H), 4.7(br. m, 2H), 4.95(br. m, 1H), 5.15(br. t, 0.25H), 5.2(br. t, 0.75H), 5.2(d, 1H), 6.95(d, 1H), 7.15(d, 1H), 7.25(br. s, 1H), 7.3(br. t, 2H), 7.45(br. s, 6H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3-Chloro-4-aminobenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (**213h**),  
was synthesized from **212h** by the methods used to

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prepare **213e** from **212e** to afford 296 mg of **213h**,  $^1\text{H}$  NMR (CDCl<sub>3</sub>)  $\delta$  1.55-1.68(m, 1H), 1.7-2.05(m, 3H), 2.3-2.5(m, 2H), 2.65-2.8(m, 1H), 2.85-2.93(m, 1H), 2.95-3.25(m, 3H), 4.44-4.65(m, 2H), 4.68-4.82(m, 1H), 4.9-4.95(d, 5 1H), 5.05-5.18(m, 2H), 5.28(s, 0.5H), 5.55-5.58(d, 0.5H), 6.52-6.58(d, 0.5H), 6.7-6.76(m, 2H), 6.82-6.85(d, 0.5H), 7.3-7.4(m, 5H), 7.52-7.58(m, 1H), 7.75(s, 0.5H), 7.8(s, 0.5H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(4-Methoxybenzoyl)amino]-6,10-dioxo-  
10 1,2,3,4,7,8,9,10-octahydro-N-(2-Benzylloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (**213i**), was synthesized from **212i** by the methods used to prepare **213e** from **212e** to afford 1.1 g of **213i**,  $^1\text{H}$  NMR  
15 (CDCl<sub>3</sub>)  $\delta$  1.55-2.05(m, 6H), 2.26-2.5(m, 2H), 2.68-2.82(m, 1H), 2.85-2.92(m, 1H), 2.95-3.25(m, 2H), 3.82(s, 1.5H), 3.85(s, 1.5H), 4.4-4.65(m, 2H), 4.7-4.78(m, 1H), 4.88-4.95(m, 1H), 5.05-5.23(m, 1H), 5.28(s, 0.5H), 5.55-5.58(d, 0.5H), 6.6-6.65(m, 1H),  
20 6.8-6.84(m, 1H), 6.9-6.95(m, 3H), 7.3-7.45(m, 4H), 7.78-7.85(m, 2H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3,5-Dichlorobenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-Benzylloxy-5-oxotetrahydrofuran-3-yl)-6H-  
25 pyridazino[1,2-a][1,2]diazepine-1-carboxamide (**213j**), was synthesized from **212j** by the methods used to prepare **213e** from **212e** to afford 367 mg of **213j**,  $^1\text{H}$  NMR (CDCl<sub>3</sub>)  $\delta$  1.55-2.05(m, 12H), 2.25(d, 1H), 2.35(m, 1H), 2.48(m, 2H), 2.75(m, 2H), 2.9(m, 1H), 2.95-3.25(m, 5H),  
30 4.45(t, 1H), 4.5-4.6(m, 4H), 4.7(m, 1H), 4.75(d, 1H),

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4.88(m, 1H), 5.05(m, 2H), 5.15(q, 1H), 5.3(s, 1H),  
5.58(d, 1H), 6.5(d, 1H), 6.9(d, 1H), 7.05(d, 1H), 7.25-  
7.35(m, 5H), 7.6(s, 2H), 7.7(s, 2H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3,5-Dichloro-4-

- 5 hydroxybenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-  
octahydro-N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6H-  
pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213k),  
was synthesized from 212k by the methods used to  
prepare 213e from 212e to afford 593 mg of 213k, <sup>1</sup>H NMR  
10 (CD<sub>3</sub>OD) δ 1.5(m, 1H), 1.6-1.7(m, 2H), 1.75-1.95(m, 4H),  
2.15(m, 2H), 2.3(m, 1H), 2.6(m, 1H), 2.7(m, 1H),  
3.05(m, 2H), 3.15(m, 1H), 3.5(m, 2H), 4.45(m, 2H),  
4.65(d, 1H), 4.7(m, 1H), 4.95(m, 1H), 5.15(m, 1H),  
5.4(s, 1H), 5.7(d, 1H), 7.3(m, 5H), 7.85(s, 2H).

- 15 [1*S*,9*S*(2*RS*,3*S*)]9-[(3-Chloro-4-acetamidobenzoyl)amino]-  
6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-Benzyloxy-5-  
oxotetrahydrofuran-3-yl)-6H-  
pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213l),  
was synthesized from 212l by the methods used to  
20 prepare 213e from 212e to afford 133 mg of 213l, <sup>1</sup>H NMR  
(CDCl<sub>3</sub>) δ 1.55-1.7(m, 1H), 1.75-2.05(m, 3H), 2.25(s,  
1.5H), 2.27(s, 1.5H), 2.3-2.48(m, 2H), 2.7-2.83(m, 1H),  
2.85-2.94(dd, 1H), 2.95-3.25(m, 2H), 4.42-4.65(m, 2H),  
4.68-4.85(m, 1H), 4.88-4.95(m, 1H), 5.05-5.18(m, 2H),  
25 5.32(s, 0.5H), 5.55-5.6(d, 0.5H), 6.48-6.55(d, 1H),  
6.88-6.92(d, 1H), 7.0-7.04(d, 0.5H), 7.15-7.2(d, 0.5H),  
7.3-7.4(m, 4H), 7.64-7.78(m, 2H), 7.88-7.94(m, 1H),  
8.45-8.56(m, 1H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3,5-Dichloro-4-

- 30 methoxybenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-



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- octahydro-N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213m), was synthesized from 212m by the methods used to prepare 213e from 212e to afford 991 mg of 213m, <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.5-2.15(m, 5H), 2.2-2.55(m, 3H), 2.6-3.3(m, 4H), 3.95(2s, 3H), 4.45-4.7(m, 2H), 4.7-4.85(m, 1H), 4.8504.95(m, 1H), 5.05-5.25(m, 1H), 5.3(s, 0.5H), 5.6(d, 0.5H), 6.55(d, 0.5H), 6.85(d, 0.5H), 7.0(d, 0.5H), 7.25-7.6(m, 5.5H), 7.75(s, 1H), 7.85(s, 1H).
- 10 [1S,9S(2RS,3S)]9-[(4-Dimethylaminobenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550f), was synthesized from 212f by the methods used to
- 15 prepare 213e from 212e to afford 420 mg of 550f as an off white solid, <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.2-1.25(br. t, 3H), 1.35(m, 1H), 1.55(br. m, 1H), 1.88-2.02(br. m, 4H), 2.3(d, 1H), 2.35(m, 1H), 2.45(m, 1H), 2.55-2.75(m, 3H), 3.0(s, 6H), 3.25(m, 1H), 3.55(m, 1H), 3.65(m, 1H),
- 20 3.75(m, 1H), 3.9(m, 1H), 4.3(t, 1H), 4.55(m, 2H), 4.68(br. m, 1H), 3.9(m, 1H), 4.3(t, 1H), 4.55(m, 2H), 4.68(br. m, 1H), 4.95(br. m, 1H), 5.1(br. m, 2H), 5.45(d, 1H), 6.5(m, 2H), 7.7(m, 2H).
- [1S,9S(2RS,3S)]9-[(3-Chloro-4-aminobenzoyl)amino]-6,10-
- 25 dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550h), was synthesized from 212h by the methods used to prepare 213e from 212e to afford 195 mg of 550h as a
- 30 white solid, <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.1-1.18(2t, 3H), 1.6-

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1.7(m, 2H), 1.88-2.05(m, 2H), 2.1-2.35(m, 3H), 2.48-2.56(m, 1H), 2.75-2.8(m, 0.75H), 2.88-3.08(m, 1.25H), 3.25-3.4(m, 1H), 3.55-3.8(m, 2H), 4.35-4.45(m, 1H), 4.55-4.62(m, 1H), 4.8-4.88(m, 1H), 4.98-5.03(m, 0.25H),  
5 5.1-5.13(m, 0.75H), 5.33(s, 0.25H), 5.58-5.6(d, 0.75H), 5.9-6.0(br. s, 2H), 6.8-6.85(d, 1H), 7.58-7.62(d, 1H), 7.82(s, 1H), 8.22-8.28(d, 1H), 8.48-8.52(d, 0.75H), 8.72-8.76(d, 0.25H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(4-Methoxybenzoyl)amino]-6,10-dioxo-  
10 1,2,3,4,7,8,9,10-octahydro-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550i),  
was synthesized from 212i by the methods used to prepare 213e from 212e to afford 135 mg of 550i, <sup>1</sup>H NMR  
15 (CDCl<sub>3</sub>) δ 1.18-1.28(2t, 3H), 1.6-1.75(m, 1.5H), 1.9-2.1(m, 3.5H), 2.22-2.3(d, 0.5H), 2.38-2.47(m, 1.5H), 2.7-2.8(m, 0.5H), 2.8-2.93(m, 1H), 2.94-3.15(m, 1.5H), 3.15-3.28(m, 1H), 3.55-3.62(q, 0.5H), 3.62-3.73(q, 0.5H), 3.78-3.88(q, 0.5H), 3.88(s, 3H), 3.9-3.95(q,  
20 0.5H), 4.33-4.4(m, 0.5H), 4.5-4.55(m, 1H), 4.68-4.76(m, 0.5H), 4.9-4.95(m, 0.5H), 5.1-5.2(m, 1.5H), 5.18(s, 0.5H), 5.48-5.52(d, 0.5H), 6.48-6.55(d, 0.5H), 6.85-6.9(m, 1H), 6.9-6.95(m, 2H), 7.34-7.38(d, 0.5H), 7.78-7.85(m, 2H).

25 [1*S*,9*S*(2*RS*,3*S*)]9-[(3,5-Dichloro-4-hydroxybenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550k),  
was synthesized from 212k by the methods used to  
30 prepare 213e from 212e to afford 174 mg of 550k as a white solid, <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.15(2t, 3H), 1.6-

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1.75(m, 2H), 1.9-2.05(m, 2H), 2.1-2.4(m, 5H), 2.5-  
2.55(m, 1H), 2.7-2.8(m, 0.5H), 2.85-3.0(m, 1H), 3.0-  
3.1(m, 0.5H), 3.55-3.7(m, 1H), 3.7-3.8(m, 1H), 4.2(t,  
0.5H), 4.35-4.45(m, 0.5H), 4.55-4.65(m, 0.5H), 4.8-  
5 4.9(m, 0.5H), 5.05(t, 0.5H), 5.15(t, 0.5H), 5.35(s,  
0.5H), 5.6(d, 0.5H), 7.95(s, 2H), 8.5(d, 0.5H), 8.65(d,  
1H), 8.75(d, 0.5H), 10.9(br. s, 1H).

[1*S*,9*S* (2*RS*,3*S*)]9-[(3-Chloro-4-acetamidobenzoyl)amino]-  
6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-ethoxy-5-  
10 oxotetrahydrofuran-3-yl)-6H-  
pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550l),  
was synthesized from 212l by the methods used to  
prepare 213e from 212e to afford 151 mg of 550l, <sup>1</sup>H NMR  
(CDCl<sub>3</sub>) δ 1.2-1.28(2t, 3H), 1.6-1.72(m, 1.5H), 1.88-  
15 2.15(m, 3.5H), 2.22-2.28(m, 0.5H), 2.28(s, 3H), 2.38-  
2.48(m, 1.5H), 2.66-2.92(m, 1.5H), 2.95-3.14(m, 1.5H),  
3.2-3.34(m, 1H), 3.56-3.63(q, 0.5H), 3.63-3.72(q,  
0.5H), 3.8-3.85(q, 0.5H), 3.9-3.95(q, 0.5H), 4.32-  
4.38(m, 0.5H), 4.5-4.62(m, 1H), 4.68-4.75(m, 0.5H),  
20 4.88-4.92(m, 0.5H), 5.08-5.2(m, 1.5H), 5.18(s, 0.5H),  
5.46-5.5(d, 0.5H), 6.5-6.55(d, 0.5H), 6.98-7.05(m, 1H),  
7.42-7.48(d, 0.5H), 7.63-7.78(m, 2.5H), 7.9-7.94(d,  
0.5H), 8.44-8.52(m, 1H).

[1*S*,9*S* (2*RS*,3*S*)]9-[(3,5-Dichloro-4-  
25 methoxybenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-  
octahydro-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-6H-  
pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550m),  
was synthesized from 212m by the methods used to  
prepare 213e from 212e to afford 301 mg of 550m as a  
30 white solid, <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.2-1.35(2t, 3H), 1.5-

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1.8(m, 2H), 1.9-2.15(5H), 2.25(d, 0.5H), 2.4-2.5(m, 2H), 2.65-2.8(m, 0.5H), 2.8-3.0(m, 0.5H), 3.0-3.2(m, 1H), 3.2-3.35(m, 0.5H), 3.55-3.65(m, 0.5H), 3.65-3.75(m, 0.5H), 3.8-3.9(m, 0.5H), 3.9-4.0(m, 0.5H), 4.4-4.45(m, 0.5H), 4.55-4.65(m, 0.5H), 4.7-4.8(m, 0.5H), 4.85-4.95(m, 0.5H), 5.05-5.2(m, 0.5H), 5.2(s, 0.5H), 5.5(d, 0.5H), 6.5(d, 0.5H), 6.9(d, 0.5H), 6.95(d, 0.5H), 7.35(d, 0.5H), 7.75(s, 1H), 7.85(s, 1H).

[3S(1S,9S)]3-(9-(3,5-Dichlorobenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (214j), was synthesized from 213j by the method used to prepare 2002 from 2001 to afford 62 mg of 214j as a white solid, <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 0.9 (t, 1H), 1.3(br. s, 1H), 1.7(br. m, 1H), 1.9(br. m, 1H), 2.1(br. s, 1H), 2.25(q, 1H), 2.35(m, 1H), 2.48(m, 2H), 2.65(t, 1H), 3.15(br. t, 1H), 3.5(br. m, 1H), 4.3(br. s, 1H), 4.55(m, 2H), 4.95(t, 1H), 5.25(br. s, 1H), 7.6(br. s, 1H), 7.85(br. s, 1H).

[3S(1S,9S)]3-(9-(3,5-Dichloro-4-hydroxybenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (214k), was synthesized from 213k by the method used to prepare 2002 from 2001 to afford 80 mg of 214k as a white solid, <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 1.6-1.7 m, 1H), 1.8-2.0(m, 2H), 2.0-2.1(m, 2H), 2.15-2.25(m, 1H), 2.3-2.4(m, 1H), 2.4-2.55(m, 2H), 2.6-2.75(m, 1H), 3.05-3.2(m, 1H), 3.4-3.6(m, 2H), 4.2-4.3(m, 1H), 4.45-4.6(m, 1H), 4.8-5.0(m, 1H), 5.1-5.2(m, 1H), 7.85(s, 2H).

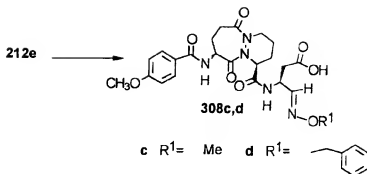
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[3S(1S,9S)]3-(9-(3-Chloro-4-acetamidobenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (214l), was synthesized from 213l by the method used to prepare 2002 from 2001 to afford 91 mg of 214l as a white solid, <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.65(br. m, 6H), 1.9(br. m, 6H), 2.15(s, 3H), 2.3(m, 3H), 2.6-2.85(m, 3H), 2.9(m, 2H), 3.0(m, 1H), 4.15(br. q, 1H), 4.4(m, 3H), 5.0(m, 1H), 5.15(m, 1H), 5.45(s, 1H), 7.8(d, 2H), 7.95(d, 1H), 8.05(s, 1H), 8.65(m, 2H), 9.65(s, 1H).

[3S(1S,9S)]3-(9-(3,5-Dichlorobenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (214m), was synthesized from 213m by the method used to prepare 2002 from 2001 to afford 105 mg of 214m as a white solid, <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 1.6-1.75(m, 1H), 1.85-1.95(m, 1H), 2.0-2.1(m, 2H), 2.15-2.25(m, 1H), 2.3-2.4(m, 1H), 2.45-2.55(m, 2H), 2.65-2.75(m, 1H), 3.4-3.55(m, 2H), 3.95(s, 3H), 4.2-4.3(m, 1H), 4.45-4.6(m, 1H), 4.9-5.0(m, 1H), 5.15-5.2(m, 1H), 7.9(s, 2H).

Compounds 308c and 308d were prepared as follows.

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[3*S*(1*S*,9*S*) 3-(9-(4-Methoxybenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-amino]-4-oxobutanoic acid, O-methyl oxime (308c), was

- 5 synthesized from **212e** via the methods used to prepare **308b** from **212e** to afford 266 mg of **308c** <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.6-1.7(m, 1H), 1.88-1.98(m, 3H), 2.02-2.15(m, 1H), 2.3-2.4(m, 1H), 2.65-2.95(m, 3H), 3.04-3.09(m, 1H), 3.12-3.25(m, 1H), 3.84(s, 3H), 3.86(s, 3H), 4.5-4.58(m, 1H), 4.88-4.95(m, 1H), 5.1-5.25(m, 2H), 6.86-6.9(d, 2H), 7.15-7.25(m, 2H), 7.36-7.4(m, 1H), 7.75-7.8(d, 2H).

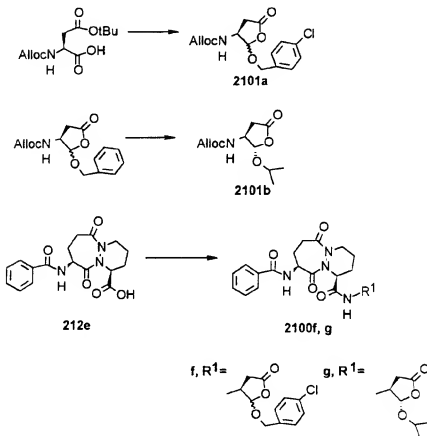
[3*S*(1*S*,9*S*) 3-(9-(4-Methoxybenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-amino]-4-oxobutanoic acid, O-benzyl oxime (308d), was

- 15 synthesized from **212e** via the methods used to prepare **308b** from **212e** to afford 270 mg of **308d**, <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.55-1.65(m, 1H), 1.8-2.1(m, 4H), 2.3-2.4(m, 1H), 2.65-2.86(m, 3H), 2.9-3.3(m, 3H), 4.5-4.58(m, 1H), 4.88-4.95(m, 1H), 5.05(s, 2H), 5.1-5.2(m, 1H), 6.82-

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6.95 (m, 2H), 7.02-7.15 (m, 2H), 7.28 (m, 5H), 7.45 (m, 1H), 7.72 (d, 2H).

Compounds **2100f**, **2100g**, **2100h**, **2100i** and **2100j** were prepared as described below.



- 5 (3*S*,2*RS*) 3-Allyloxycarbonylamino-2-(4-chlorobenzyl)oxy-5-oxotetrahydrofuran (**2101a**), was synthesized from allyloxycarbonylamino-β-tert-butyl aspartate by the methods employed by Chapman (Bioorg. & Med. Chem. Lett., 2, pp.615-618 (1992)) to prepare (3*S*,2*RS*) 3-
- 10 allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydrofuran

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using 4-chlorobenzyl alcohol instead of benzyl alcohol to afford 1.84 g of **2101a** as a crystalline solid.

[1*S*,9*S*(2*RS*,3*S*)] 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-(4-chlorobenzyl)oxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide (**2100f**), was synthesized from **212e** by the methods used to prepare **213e** from **212e** using **2101a** to afford 380 mg of **2100f**, <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.8-2.0(m, 10H), 2.30(d, 1H), 2.31-2.5(m, 3H), 2.7-2.9(m, 3H), 3.05(m, 2H), 3.1-3.2(m, 4H), 4.45(q, 1H), 4.5-4.6(m, 3H), 4.7(d, 2H), 4.85(d, 1H), 4.9(t, 1H), 5.2(t, 1H), 5.15(m, 2H), 5.25(s, 1H), 5.55(d, 1H), 6.5(d, 1H), 6.9(d, 1H), 6.95(d, 1H), 7.25(m, 3H), 7.35(t, 2H), 7.45(m, 2H), 7.55(1H), 7.8(m, 3H).

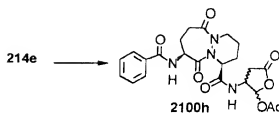
(3*S*,2*RS*) 3-Allyloxycarbonylamino-2-*anti*-isopropoxy-5-oxotetrahydrofuran (**2101b**), was synthesized from (3*S*,2*RS*) 3-allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydrofuran via the method used to prepare **2100d** from **214e** using H<sub>2</sub>SO<sub>4</sub> instead of pTSA to afford **2101b**.

[1*S*,9*S*(2*RS*,3*S*)] 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-*anti*-isopropoxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide (**2100g**), was synthesized from **212e** by the methods used to prepare **213e** from **212e** using **2101b** to afford 31 mg of **2100g**, <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.19 (d), 1.94 (br s), 2.00-2.12 (m), 2.24 (d), 2.42 (dd), 2.71-2.83 (m), 3.02 (dd), 3.12-3.27 (overlapping m), 3.93 (m), 4.32-4.37 (m),



- 563 -

4.52-4.63 (m), 4.90-4.95 (m), 5.12-5.20 (m), 5.28 (s),  
6.93 (d), 7.10 (d), 7.41-7.50 (m), 7.51-7.58 (m), 7.84  
(d).

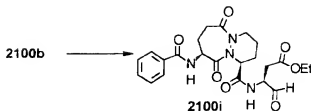


[1*S*,9*S*(2*RS*,3*RS*)] 9-Benzoylamino-6,10-dioxo-

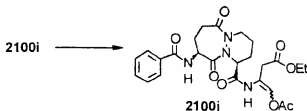
- 5 1,2,3,4,7,8,9,10-octahydro-N-(2-acetoxy-5-  
oxotetrahydrofuran-3-yl)-6H-  
pyridazino[1,2-a][1,2]diazepine-1-carboxamide (2100h).

A solution of 214e (287 mg, 0.65 mmol) in pyridine (5  
mL) was treated with Ac<sub>2</sub>O (0.4 mL, 3.62 mmol). After 6  
10 hours, the reaction mixture was poured into 5% NaHSO<sub>4</sub>  
and extracted 3 times with EtOAc. The combined  
organics were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and  
concentrated *in vacuo*. Chromatography (SiO<sub>2</sub>, EtOAc)  
afforded 119 mg of 2100h, <sup>1</sup>HNMR (CDCl<sub>3</sub>, mixture of four  
15 diastereoisomers) δ 1.80-2.05(m), 2.12(s), 2.13(s),  
2.19(s), 2.22(d), 2.67-2.75(m), 2.80-2.95(m), 3.00-  
3.20(m), 3.21-3.33(m), 3.50-3.95(four discrete  
multiplets), 4.19(m), 4.55(m), 4.57-4.65(m), 4.69(m),  
4.85-4.95(m), 5.04(m), 5.10(s), 5.10-5.22(m), 6.46(d),  
20 6.03(s), 6.50(d), 6.58(d), 6.75(d), 6.95-7.05(m),  
7.22(m), 7.30(m), 7.71(d), 7.75-7.83(m).

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- [3S(1S,9S)]3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid ethyl ester (2100i). To a solution of
- 5 2100b (1.5 g, 2.7 mmol) in CH<sub>3</sub>CN (10 mL) was added 1N HCl at ambient temperature. After 6 hours solid NaHCO<sub>3</sub> was added and the product extracted with EtOAc, dried over MgSO<sub>4</sub> and concentrated in vacuo. Chromatography (SiO<sub>2</sub>, 30-100% CH<sub>2</sub>Cl<sub>2</sub> in EtOAc) afforded 123 mg of
- 10 2100i, <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.25(t, 3H), 1.6-1.8(m, 1H), 1.9-2.2(m, 5H), 2.4-2.5(m, 1H), 2.75-2.9(m, 2H), 3.0-3.1(m, 2H), 3.2-3.25(m, 1H), 4.05-4.2(m, 1H), 4.5-4.7(m, 1H), 5.1-5.25(m, 1H), 7.0-7.2(m, 2H), 7.4-7.45(m, 2H), 7.5(t, 1H), 7.8(t, 2H), 9.5(s, 1H).



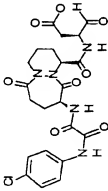
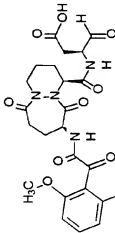
- 15 [3S(1S,9S)]3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-acetoxy-3-butenic acid ethyl ester (2100j), was synthesized from 2100i via the method used to prepare

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2100h from 214e to afford 347 mg of 2100j,  $^1\text{H}$  NMR  
( $\text{CDCl}_3$ )  $\delta$  1.3(t, 3H), 1.6-1.8(m, 2H), 1.9-2.25(m, 4H),  
2.25(s, 3H), 2.3-2.45(m, 1H), 2.6-3.0(m, 1H), 3.0-  
3.25(m, 2H), 3.4-3.45(m, 2H), 4.1-4.2(m, 2H), 4.55-  
5 4.7(m, 1H), 5.1-5.25(m, 1H), 6.8(s, 1H), 7.0-7.1(m,  
2H), 7.5(t, 1H), 7.8(t, 2H), 9.5(s, 1H).

Compounds 500 and 501 are described in Table  
23. These compounds were prepared by methods similar  
to the methods used to prepare compounds 404-449 (see,  
10 Example 11).

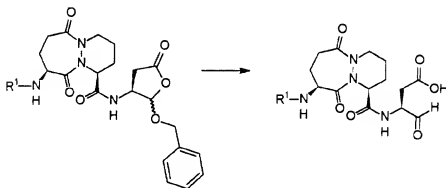
Table 23

| Compound | Structure   | MF           | MW     | HPLC RT min<br>(method)<br>Purity | MS<br>(M+H) <sup>+</sup> |
|----------|---|--------------|--------|-----------------------------------|--------------------------|
| 500      |  | C22H24ClN5O8 | 521.92 | 11.448 (A)<br>0.991               | 523.1                    |
| 501      |  | C24H28N4O10  | 532.51 | 10.13 0.97                        | 533                      |

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The compounds described below (213m, 213n, 213o, 213p, 213q, 213r, 213s, 213t, 213u, 213v, 213w, 213x, and 214w), were prepared by methods similar to the methods used to prepare compounds 213b-f.

Compounds 419, 415, 450, 456, 475, 404, 486, 487, 417, 408 and 418 may also be prepared as described below.



213m-x  
214w, 404, 408, 415,

10





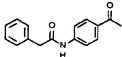
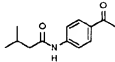

417, 418, 419, 450,

15



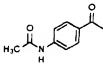
456, 475, 486, 487

| compound  | R <sup>1</sup> |
|-----------|----------------|
| 213m, 419 | MeOC(O) -      |
| 213n, 415 |                |

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|           |  |
|-----------|--|
| 213o, 450 |   |
| 213p, 456 |   |
| 213q, 475 |   |
| 213r, 404 |   |
| 213s, 486 |   |
| 213t, 487 |   |
| 213u, 417 |  |

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|            |   |
|------------|---|
| 213v, 408  |  |
| 213w, 214w |  |
| 213x, 418  |  |

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(3,4-methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213n), was isolated as a mixture of diastereomers (syn:anti isomer ratio 6:4) (1.43g, 82%) as a white solid: mp. 206-10°C; IR (KBr) 3288, 1787, 1680, 1657, 1651, 1619, 1548, 1440, 1256, 1135; <sup>1</sup>H NMR (D<sub>6</sub>-DMSO) δ 8.75 (0.4H, d), 8.55 (0.6H, d), 8.45 and 8.43 (1H, 2 x d), 7.50 (1H, d), 7.42 (1H, s), 7.40-7.27 (5H, m), 7.01 (1H, d), 6.11 (2H, s), 5.67 (0.6H, d), 5.43 (0.4H, s), 5.10-5.00 (1H, m), 4.90-4.59 (3.5H, m), 4.45-4.25 (1.5H, m), 3.47-3.20 (1H, m), 3.20-2.70 (2H, m), 2.65-2.35 (1H, m), 2.35-2.00 (3H, m), 2.00-1.75 (2H, m), 1.65-1.40 (2H, m). Anal. Calcd for C<sub>29</sub>H<sub>30</sub>N<sub>4</sub>O<sub>9</sub>: C, 60.20; H, 5.23; N, 9.68. Found: C, 60.08; H, 5.32; N, 9.50. MS (ES<sup>+</sup>)

- 570 -

580 ( $M^+ + 2$ , 35%), 579 ( $M^+ + 1$ , 100), 404 (5), 367 (5),  
236 (7), 107 (5).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3-Acetamido)benzamido]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-

- 5 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213o),  
anti-isomer as a white foamy solid (0.73g, 69%): mp.  
135-40°C;  $[\alpha]_D^{25} -37.3^\circ$  (c 0.1, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3452,  
3310, 1790, 1664, 1659, 1549, 1425, 1258, 1121;  
10 <sup>1</sup>H NMR (D<sub>6</sub>-DMSO)  $\delta$  10.11 (1H, s), 8.77 (1H, d), 8.57  
(1H, d), 8.01 (1H, s), 7.76 (1H, d), 7.55 (1H, d),  
7.45-7.25 (6H, m), 5.43 (1H, s), 5.08-5.00 (1H, m),  
4.95-4.73 (1H, m), 4.76 and 4.68 (2H, dd), 3.40-3.20  
(1H, m), 3.09 (1H, dd), 3.02-2.75 (1H, m), 2.45-2.06  
15 (4H, m), 2.06 (3H, s), 2.00-1.75 (2H, m), 1.70-1.40  
(2H, m). Anal. Calcd for C<sub>30</sub>H<sub>33</sub>N<sub>5</sub>O<sub>8</sub>•0.75H<sub>2</sub>O: C, 59.54;  
H, 5.75; N, 11.57. Found: C, 59.40; H, 5.62; N, 11.50.  
MS (ES<sup>+</sup>) 593 ( $M^+ + 2$ , 33%), 592 ( $M^+ + 1$ , 100), 574 (7),  
487 (7), 475 (6), 385 (9), 373 (26), 318 (14), 296  
20 (11), 266 (10), 221 (22).

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(4-hydroxybenzoyl)amino-

1,2,3,4,7,8,9,10-octahydro-6H-

pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213p),

- 25 was isolated as a foam (1.2g, 77%):  $[\alpha]_D^{20} -115^\circ$  (c  
0.20, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3368, 2946, 1794, 1654, 1609,  
1540, 1505, 1421, 1277, 1175, 1119, 980; <sup>1</sup>H NMR (D<sub>6</sub>-  
DMSO)  $\delta$  10.1 (1H, s), 8.80 (0.5H, d, J = 6.6), 8.60  
(0.5H, d, J = 7.2), 8.40-8.36 (1H, 2d), 7.82 (2H, d, J  
30 = 8.0), 7.41 (5H, bs), 6.86 (2H, d, J 8.6), 5.72 (0.5H,



- 571 -

d,  $J = 5.0$ ), 5.49 (0.5H, bs), 5.13-5.07 (1H, m), 4.95-4.65 (2.5H, m), 4.49-4.38 (2.5H, m), 3.49-3.30 (2H, m), 3.21, 2.79 (2H, m), 2.40-1.41 (7H, m). MS ( $ES^+$ ) 551.

[1*S*,9*S*(2*RS*,3*S*)]N-(2-Benzylloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(indol-2-oylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213q), was isolated as a white glassy solid (80%): mp. 145-149°C;  $[\alpha]_D^{23} -56.0^\circ$  (c 0.05,  $CH_2Cl_2$ ); IR (KBr) 3399-3319, 1791, 1657, 1543, 1420, 1253, 1119;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  9.54 (1H, s), 7.65 (1H, d,  $J = 7.9$ ), 7.51 (1H, d,  $J = 6.9$ ), 7.44-7.25 (7H, m), 7.18-7.06 (3H, m), 5.30-5.20 (1H, m), 5.27 (1H, s), 4.84 (1H, m), 4.79 (1H, d,  $J = 11.4$ ), 4.56 (1H, d,  $J = 11.3$ ), 4.47 (2H, m), 3.28 (1H, m), 3.10-2.97 (2H, m), 2.71 (1H, m), 2.47-2.37 (1H, m), 2.26 (1H, d,  $J = 17.9$ ), 2.09 (1H, m), 1.83, 1.70, 1.51 (4H, 3m).

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Benzylloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-9-(2-toluoylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213r), was isolated as a mixture of diastereomers (syn:anti isomer ratio 55:45) as a white foamy solid (1.46g, 89%): mp. 106-10°C; IR (KBr) 3306, 2947, 1791, 1659, 1650, 1535, 1421, 1256, 1122;  $^1H$  NMR ( $D_6$ -DMSO)  $\delta$  8.76 (0.45H, d), 8.56 (0.55H, d), 8.49 and 8.47 (1H, 2 x d), 7.41-7.19 (9H, m), 5.67 (0.55H, d), 5.43 (0.45H, s), 5.11-5.02 (1H, m), 4.86-4.55 (3.5H, m), 4.45-4.25 (1.5H, m), 3.40-3.20 (1H, m), 3.20-2.70 (2H, m), 2.65-2.40 (1H, m), 2.34 (3H, s), 2.30-1.70 (5H, m), 1.65-1.40 (2H, m). Anal. Calcd for  $C_{29}H_{32}N_4O_7$ : C, 62.66; H, 5.95; N, 10.08. Found: C, 62.91; H, 6.00;

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N, 9.70. MS ( $ES^+$ ) 550 ( $M^+ + 2$ , 43%), 549 ( $M^+ + 1$ , 100), 374 (3), 280 (4), 279 (20), 118 (5).

- [1*S*,9*S*(2*RS*,3*S*)]N-(2-Benzylloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-9-[4-(phenylacetamido)benzamido]-6H-pyridazino[1,2-a][1,2]diazepin-1-carboxamide (213s), was isolated as the anti-isomer as a white foamy solid (0.64g, 77%): mp. 137-41°C;  $[\alpha]_D^{21}$  -48.2° (c 0.05, CH<sub>3</sub>OH); IR (KBr) 3477, 3314, 1791, 1659, 1599, 1529, 1499, 1406, 1256, 1122; <sup>1</sup>H NMR (D<sub>6</sub>-DMSO) δ 10.45 (1H, s), 8.76 (1H, d), 8.50 (1H, d), 7.86 (2H, d), 7.69 (2H, d), 7.41-7.20 (10H, m), 5.43 (1H, s), 5.08-4.98 (1H, m), 4.90-4.73 (1H, m), 4.76 and 4.68 (2H, dd), 3.67 (2H, s), 3.40-3.20 (1H, m), 3.09 (1H, dd), 3.02-2.75 (1H, m), 2.39 (1H, dd), 2.30-2.00 (3H, m), 2.00-1.75 (2H, m), 1.70-1.40 (2H, m). Anal. Calcd for C<sub>36</sub>H<sub>37</sub>N<sub>5</sub>O<sub>8</sub>•0.5H<sub>2</sub>O: C, 63.90; H, 5.66; N, 10.35. Found: C, 63.68; H, 5.67; N, 10.24. MS ( $ES^+$ ) 669 ( $M^+ + 2$ , 40%), 668 ( $M^+ + 1$ , 100), 640 (12), 435 (18), 425 (23), 403 (33), 328 (17), 302, (32), 274 (22), 197 (16), 138 (17).

- [1*S*,9*S*(2*RS*,3*S*)]N-(2-Benzylloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-[4-(3-methylbutan-1-oylamino)benzamido]-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213t), was isolated as a white foamy solid (0.63g, 80%): mp. 159-64°C;  $[\alpha]_D^{21}$  -37.0° (c 0.05, CH<sub>3</sub>OH); IR (KBr) 3463, 3321, 1790, 1680, 1658, 1650, 1644, 1595, 1525, 1501, 1408, 1251, 1113, 933; <sup>1</sup>H NMR (D<sub>6</sub>-DMSO) δ 10.13 (1H, s), 8.76 (1H, d), 8.48 (1H, d), 7.85 (2H, d), 7.68 (2H, d),

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7.40-7.25 (5H, m), 5.43 (1H, s), 5.08-4.95 (1H, m),  
 4.92-4.73 (1H, m), 4.76 and 4.68 (2H, dd), 3.40-3.20  
 (1H, m), 3.09 (1H, dd), 3.02-2.75 (1H, m), 2.39 (1H,  
 dd), 2.35-2.00 (6H, m), 2.00-1.75 (2H, m), 1.70-1.40  
 (2H, m), 0.93 (6H, d). Anal. Calcd for

$C_{33}H_{39}N_5O_8 \cdot 0.5H_2O$ : C, 61.67; H, 6.27; N, 10.90. Found:  
 C, 61.49; H, 6.24; N, 10.86. MS ( $ES^+$ ) 635 ( $M^+ + 2$ ,  
 39%), 634 ( $M^+ + 1$ , 100), 484 (10), 427 (9), 274 (18),  
 268 (37), 204 (19), 117 (13).

10 [1*S*,9*S*(2*RS*,3*S*)] N-(2-Benzylloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-9-(3,4,5-trimethoxybenzoylamino)-6H-

pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213u),

was isolated as a white solid (81%): mp. 120-132°C; IR

15 (KBr) 3361-3334, 1792, 1659, 1585, 1536, 1499, 1457, 1416, 1340, 1236, 1126, 989;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.39-7.29 (6H, m), 7.12 (1H, s), 7.03 (1H, s), 6.92, 6.83, 6.48 (approx 3H, 3d, J = 8.1, 7.5, 8.1), 5.57 (d, J = 5.3), 5.27 (1H, s), 5.23-5.06, 4.91-4.71, 4.64-4.43, (6H,  
 20 3m), 3.92, 3.91, 3.89, 3.88 (9H, 4s), 3.32-2.70, 2.52-2.08, 1.91, 1.63 (1H, 4m).

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Benzylloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(naphth-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-

25 carboxamide (213v), was isolated as a white solid

(78%): mp. 121-7°C; IR (KBr) 3534-3331, 1791, 1659,

1528, 1420, 1256, 1122;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  8.34-8.29 (1H, m), 7.98-7.87 (2H, m), 7.68-7.45 (4H, m), 7.34-7.24 (5H, m), 7.04 (d, J = 6.8), 6.78 (d, J = 7.8), 6.66 (d, J = 7.7), 6.48 (2H, d, J = 7.5) 5.56 (d, J = 5.4), 5.15

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(1H, s), 5.30-5.14, 5.0, 4.89 (d, J = 11.2), 4.71-4.41 (6H), 3.18-2.80, 2.50-2.27, 2.08-1.60 (1H, 3m).

- [1S,9S(2RS,3S)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(4-hydroxy-3,5-dimethylbenzoyl)amino-  
 5 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213w),  
 was isolated as a mixture of diastereoisomers (65/35) as a white solid (0.9g, 65%): mp. 110-115°C (decomp.); IR (KBr) 3409, 2945, 1792, 1658, 1606, 1534, 1486,  
 10 1420, 1330, 1276, 1209, 1122, 980, 960; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.66 (0.35H, d, J = 6.9), 7.46-7.20 (7H, m), 6.93 (0.35H, d, J = 7.7), 6.85 (0.65H, d, J = 7.6), 6.73 (0.65H, d, J = 7.6), 5.96 (0.35H, bs), 5.85 (0.65H, bs), 5.56 (0.65H, d, J = 5.2), 5.28 (0.35H, bs), 5.20-  
 15 4.98 (2H, m), 4.96-4.40 (4H, m), 3.28-2.55 (3H, m), 2.53-2.32 (1H, m), 2.23 (6H, 2s), 2.03-1.40 (7H, m). MS (ES<sup>-</sup>) 577, (ES<sup>+</sup>) 579.

- [1S,9S(2RS,3S)] 9-[4-(Acetylamino)benzoylamino]-N-(2-benzyloxy-5-oxo-tetrahydrofuran-3-yl)-6,10-dioxo-  
 20 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboximide (213x),  
 was isolated as a colourless powder (691mg, 86%): mp. 150-70°C; [α]<sub>D</sub><sup>22</sup> -10.1° (c 0.10, Me<sub>2</sub>CO); IR (KBr) 3313, 1791, 1679, 1654, 1597, 1528, 1501, 1457, 1407, 1371,  
 25 1315, 1255, 1184, 1122, 933; <sup>1</sup>H NMR (d<sub>6</sub>-DMSC) δ 8.75 (1H, d), 8.47 (1H, d), 7.84 (2H, d), 7.66 (2H, d), 7.35 (5H, m), 5.43 (1H, s), 5.06-5.00 (1H, m), 4.90-4.64 (3H, m), 4.46-4.26 (2H, m), 3.16-2.86 (2H, m), 2.45-2.05 (5H, m), 2.07 (3H, s), 2.00-1.84 (2H, m), 1.68-1.56 (2H, m);  
 30 Anal. Calcd for C<sub>30</sub>H<sub>33</sub>N<sub>5</sub>O<sub>8</sub>•H<sub>2</sub>O: C, 59.11; H, 5.79; N,

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11.49. Found: C, 59.38; H, 5.66; N, 11.31; M.S. ( $\text{ES}^+$ ) 614 (100%), 592 ( $\text{M}^+ + 1.66$ ).

- [3S(1S,9S)] 3-[6,10-Dioxo-9-(3,4-methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-  
5 6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (415), was prepared by a similar method as compound 214e to afford a white solid (297mg, 84%): mp. 158-62°C;  $[\alpha]_{\text{D}}^{24}$  -109.5° (c 0.1,  $\text{CH}_3\text{OH}$ ); IR (KBr) 3700-2500 (br), 1783, 1659, 1650, 1538, 1486,  
10 1439, 1257, 1037;  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.48 (1H, dd), 7.35 (1H, d), 6.88 (1H, d), 6.03 (2H, s), 5.25-5.15 (1H, m), 5.02-4.90 (1H, m), 4.63-4.45 (2H, m), 4.30-4.20 (1H, m), 3.57-3.30 (1H, m), 3.20-3.05 (1H, m), 2.75-2.10 (5H, m), 2.10-1.60 (4H, m). MS ( $\text{ES}^+$ ) 488 ( $\text{M}^+$ , 25%),  
15 487 ( $\text{M}^+ - 1$ , 100), 443 (8), 387 (3), 315 (5), 150 (6), 127 (5), 113 (8). Accurate mass calculated for  $\text{C}_{22}\text{H}_{25}\text{N}_4\text{O}_9$  ( $\text{MH}^+$ ): 489.1621. Found 489.1648.

- [3S(1S,9S)] 3-(9-[(3-Acetamido)benzamido]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-  
20 pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (450), was prepared by a similar method as compound 214e to afford a white foamy solid (378mg, 94%): mp. 175-9°C;  $[\alpha]_{\text{D}}^{22}$  -91.7° (c 0.1,  $\text{CH}_3\text{OH}$ ); IR (KBr) 3700-2500 (br), 3319, 1659, 1590, 1553, 1427,  
25 1260;  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  8.01 (1H, d), 7.74 (1H, dd), 7.56 (1H, d), 7.45-7.35 (1H, m), 5.25-5.15 (1H, m), 5.05-4.90 (1H, m), 4.60-4.45 (2H, m), 4.30-4.20 (1H, m), 3.55-3.30 (1H, m), 3.20-3.00 (1H, m), 2.75-2.20 (5H, m), 2.14 (3H, s), 2.20-1.60 (4H). Anal. Calcd for  
30  $\text{C}_{23}\text{H}_{27}\text{N}_5\text{O}_8 \cdot 1.5\text{H}_2\text{O}$ : C, 52.27; H, 5.72; N, 13.25. Found:

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C, 52.31; H, 5.86; N, 12.85. MS (ES<sup>+</sup>) 501 (M<sup>+</sup>, 26%), 500 (M<sup>+</sup> - 1, 100), 328 (2), 149 (3), 113 (3).

[3S(1S,9S)] 3-[4-(Hydroxybenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-

- 5 pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (456), was prepared by a similar method as compound 214e to afford a white solid (0.73g, 72%): mp. >260°C; [α]<sub>D</sub><sup>20</sup> -66° (c 0.34, MeOH); IR (KBr) 3401, 2946, 1651, 1609, 1584, 1506, 1426, 1277, 1257, 10  
1177; <sup>1</sup>H NMR (D<sub>6</sub>-DMSO) δ 10.2 (1H, very bs), 9.17 (1H, bs), 8.65 (1H, s), 8.37 (1H, d, J 5.4), 7.81 (2H, d, J = 8.2), 6.87 (2H, d, J = 8.4), 5.24 (1H, m), 4.92-4.86 (1H, m), 4.41-4.32 (2H, m), 3.68-3.21 (3H, m), 3.12-2.79 (1H, m), 2.50-1.42 (7H, m). MS (ES<sup>+</sup>) 459.

- 15 [3S(1S,9S)] 3-[6,10-Dioxo-9-(indol-2-oylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (475), was prepared by a similar method to that described for compound 214e to afford a  
20 white solid (79%): mp. 150°C (softens) 190-210°C; [α]<sub>D</sub><sup>23</sup> -97.5° (c 0.1, CH<sub>3</sub>OH); IR (KBr) 3319, 1658, 1650, 1549, 1421, 1256; <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.61 (1H, d, J = 8.0), 7.43 (1H, d, J = 8.1), 7.21 (2H, m), 7.05 (1H, m), 5.21 (1H, m), 5.07-4.77 (1H, m), 4.54 (2H, m), 4.23 (1H, m),  
25 3.46 (1H, m), 3.14 (1H, m), 2.66-1.71 (9H, m). MS (ES<sup>+</sup>, m/z), 482 (M<sup>+</sup> - 1, 100%).

[3S(1S,9S)] 3-[6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-9-(2-toluoylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (404), was prepared by

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a similar method as compound **214e** to afford a white solid (0.79g, 86%): mp. 156-9°C;  $[\alpha]_D^{25}$  -119.7° (c 0.1, CH<sub>3</sub>OH); IR (KBr) 3700-2500 (br), 3387, 3309, 2956, 1785, 1659, 1650, 1535, 1422, 1278; <sup>1</sup>H NMR (CD<sub>3</sub>CD) δ

7.46-7.15 (4H, m), 5.25-5.15 (1H, m), 5.02-4.90 (1H, m), 4.58-4.45 (2H, m), 4.30-4.20 (1H, m), 3.55-3.30 (1H, m), 3.20-3.05 (1H, m), 2.80-2.20 (4H, m), 2.41 (3H, s), 2.20-1.60 (5H, m). MS (ES<sup>+</sup>) 458 (M<sup>+</sup>, 27%), 457 (M<sup>+</sup> - 1, 100), 413 (13), 339 (8), 285 (5), 134 (6), 127 (11). Accurate mass calculated for C<sub>22</sub>H<sub>27</sub>N<sub>4</sub>O<sub>7</sub> (MH<sup>+</sup>): 459.1880. Found 459.1854.

**[3S(1S,9S)] 3-{6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-9-[4-(phenylacetamido)benzamido]-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido}-4-oxobutanoic acid (486)**, was prepared by a similar method as compound **214e** to afford a white solid (325mg, 89%): mp. 165-9°C;  $[\alpha]_D^{22}$  -69.1° (c 0.1, CH<sub>3</sub>OH); IR (KBr) 3700-2500 (br), 3318, 1658, 1599, 1530, 1505, 1407, 1258; <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.85 (2H, d), 7.69 (2H, d), 7.38-7.20 (5H, m), 5.25-5.15 (1H, m), 5.05-4.90 (1H, m), 4.57-4.45 (2H, m), 4.30-4.20 (1H, m), 3.70 (2H, s), 3.55-3.30 (1H, m), 3.20-3.00 (1H, m), 2.75-1.60 (9H, m). Anal. Calcd for C<sub>29</sub>H<sub>31</sub>N<sub>5</sub>O<sub>8</sub>·1.5H<sub>2</sub>O: C, 57.61; H, 5.67; N, 11.58. Found: C, 57.81; H, 5.74; N, 11.47. MS (ES<sup>+</sup>) 577 (M<sup>+</sup>, 33%), 576 (M<sup>+</sup> - 1, 100), 502 (2).

**[3S(1S,9S)] 3-{6,10-Dioxo-9-[4-(3-methylbutan-1-oylamino)benzamido]-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido}-4-oxobutanoic acid (487)**, was prepared by a similar

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method as compound **214e** to afford a white foamy solid (335mg, 93%): mp. 176-80°C;  $[\alpha]_D^{22}$  -88.0° (c0.1, CH<sub>3</sub>OH); IR (KBr) 3700-2500 (br), 3321, 2960, 1781, 1660, 1597, 1529, 1407, 1258, 1187; <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.86 (2H, d), 7.69 (2H, d), 5.25-5.15 (1H, m), 5.05-4.90 (1H, m), 4.60-4.45 (2H, m), 4.30-4.20 (1H, m), 3.57-3.30 (1H, m), 3.20-3.00 (1H, m), 2.75-1.60 (12H, m), 1.00 (6H, d). Anal. Calcd for C<sub>26</sub>H<sub>33</sub>N<sub>5</sub>O<sub>8</sub>•H<sub>2</sub>O: C, 55.61; H, 6.28; N, 12.45. Found: C, 56.00; H, 6.37; N, 12.15. MS (ES<sup>+</sup>) 543 (M<sup>+</sup>, 31%), 542 (M<sup>+</sup> - 1, 100), 498 (2), 468 (3).

[3S(1S,9S)] 3-[6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-9-(3,4,5-trimethoxybenzoylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (**417**), was prepared by a similar method to that described for compound **214e** to afford a white solid (0.63g, 92%): mp. 145-155°C (approx., not sharp);  $[\alpha]_D^{27}$  -114.6° (c 0.11, CH<sub>3</sub>OH); IR (KBr) 3327, 1658, 1586, 1548, 1501, 1416, 1341, 1238, 1126; <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.22 (2H, s), 5.21 (1H, m), 5.00 (1H, m), 4.56, 4.49 (2H, 2m), 4.25 (1H, m), 3.88 (6H, s), 3.80 (3H, s), 3.55-3.43 (1H, m), 3.12 (1H, m), 2.71-1.70 (9H, m). Anal. Calcd for C<sub>24</sub>H<sub>30</sub>N<sub>4</sub>O<sub>10</sub>•2H<sub>2</sub>O: C, 50.52; H, 6.01; N, 9.82. Found: C, 50.49; H, 6.05; N, 9.68. MS (ES<sup>+</sup>, m/z) 533 (M<sup>+</sup> - 1, 100%).

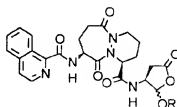
[3S(1S,9S)] 3-[6,10-Dioxo-9-(naphth-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (**408**), was prepared by a similar method to that described for compound **214e** to afford a



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white solid (73%): mp. 157-165°C (not sharp);  $[\alpha]_D^{27}$  -140.5° (c 0.1, CH<sub>3</sub>OH); IR (KBr) 3325, 1658, 1531, 1420, 1278, 1257; <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 8.33-8.28 (1H, m), 8.01-7.78 (2H, m), 7.71 (1H, d, J = 6.0), 7.59-7.52 (3H, m), 5.27 (1H, m), 5.12-5.03 (1H, m), 4.55 (2H, m), 4.25 (1H, m), 3.64-3.43 (1H, m), 3.24-3.12 (1H, m), 2.80-1.67 (9H, m). Anal. Calcd for C<sub>25</sub>H<sub>26</sub>N<sub>4</sub>O<sub>7</sub>·2H<sub>2</sub>O: C, 56.60; H, 5.70; N, 10.56. Found: C, 56.70; H, 5.80; N, 10.33. MS (ES<sup>+</sup>, m/z), 493 (M<sup>+</sup> - 1, 100%).

- 10 [3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-4-(hydroxy-3,5-dimethylbenzoyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (214w), was prepared by a similar method as compound 214e to afford 210mg (62%) of a
- 15 white solid: mp. >260°C;  $[\alpha]_D^{20}$  -93° (c 0.20, MeOH); IR (KBr) 3401, 2948, 1651, 1604, 1559, 1486, 1421, 1325, 1276, 1210; <sup>1</sup>H NMR (D<sub>6</sub>-DMSO) δ 9.39 (1H, bs), 8.29 (1H, d, J = 5.9), 7.55 (2H, s), 6.64 (1H, d, J = 6.1), 5.79 (1H, s), 5.25-5.21 (1H, m), 1.90-1.82 (1H, m), 4.41-
- 20 3.69 (2H, m), 3.47-3.20 (3H, m), 2.97-2.91 (1H, m), 2.23 (6H, s), 2.25-1.60 (7H, m).



550q R = Et

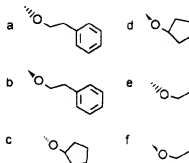
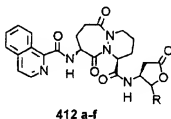
213y R = Bn

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Ethoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-

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octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550q), was synthesized via methods used to prepare 213e to afford 550q.

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Benzoyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-ylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213y), was synthesized via methods used to prepare 213e to afford 213y.



[1*S*,9*S*(2*S*,3*S*)] N-(2-Phenethoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-ylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (412a) was synthesized via methods used to prepare 550q using 513a-1 to afford 412a.

[1*S*,9*S*(2*R*,3*S*)] N-(2-Phenethoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-ylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (412b) was synthesized via

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methods used to prepare 550q using 513a-2 to afford 412b.

[1*S*,9*S*(2*S*,3*S*)] N-(2-Cyclopentoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-ylamino)-

- 5 1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (412c) was synthesized via methods used to prepare 550q using 513b-1 to afford 412c.

[1*S*,9*S*(2*R*,3*S*)] N-(2-Cyclopentoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-ylamino)-

- 10 1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (412d) was synthesized via methods used to prepare 550q using 513b-2 to afford 412d: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.5 (1H, d),  
15 8.9 (1H, d), 8.5 (1H, d), 7.9-7.8 (2H, m), 7.8-7.65 (2H, m), 6.55 (1H, d), 5.55 (1H, d), 5.25-5.1 (2H, m), 4.75-4.65 (1H, m), 4.65-4.6 (1H, m), 4.4-4.3 (1H, m), 3.25-3.15 (1H, m), 3.15-3.05 (1H, m), 2.95-2.8 (2H, m), 2.55-2.4 (2H, m), 2.15-1.5 (14H, m).

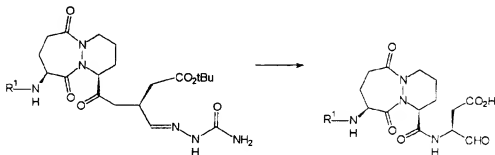
- 20 [1*S*,9*S*(2*S*,3*S*)] N-(2-Ethoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-ylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2] diazepine-1-carboxamide, (412e) was synthesized via methods used to prepare 550q using 513f-1 to afford 412e.

- 25 [1*S*,9*S*(2*R*,3*S*)] N-(2-Ethoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-ylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2] diazepine-1-

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carboxamide, (412f) was synthesized via methods used to prepare 550q using 513f-2 to afford 412f.

Compounds 410 and 412 were prepared via methods used to prepare 605 from 604.



5

502y, 502z

410, 412

| compound  | R <sup>1</sup> |
|-----------|----------------|
| 502y, 410 |                |
| 502z, 412 |                |

[3S(1S,9S)] 3-[(6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-  
 10 6H-pyridazino[1,2-a][1,2]diazepine-9-(thiophene-3-yl-  
 carbonylamino)-1-carboxamido]-4-oxobutanoic acid (410),  
 was purified by flash chromatography (5-25% methanol in  
 dichloromethane) to give 296mg (94%) of a colourless  
 solid: mp. 90-200°C; IR (KBr) 3338, 3096, 2950, 1787,  
 15 1726, 1657, 1546, 1420, 1279, 1258, 1125, 1092, 984,

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933;  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  8.41 (1H, d), 8.13 (1H, d), 7.54-7.41 (3H, m), 7.20 (1H, d), 5.19-5.11 (1H, m), 4.54-4.30 (1H, m), 3.27 (1H, m), 3.18-3.03 (1H, m), 2.81-2.64 (2H, m), 2.56-1.59 (7H, m). Anal. Calcd for

- 5  $\text{C}_{19}\text{H}_{22}\text{N}_4\text{O}_7\text{S} \cdot 2.5\text{H}_2\text{O}$ : C, 46.05; H, 5.49; N, 11.31. Found: C, 46.36; H, 5.25; N, 11.10. MS ( $\text{ES}^+$ ) 449 ( $\text{M} - 1$ , 80%), 113 (100). Accurate mass calculated for  $\text{C}_{19}\text{H}_{23}\text{N}_4\text{O}_7\text{S}$  ( $\text{MH}^+$ ): 451.1287. Found: 451.1295.

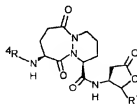
- [3S(1S,9S)] 3-[6,10-Dioxo-9-(isoquinolin-1-ylamino)-  
10 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (412) was prepared by a similar method to that described for compound 605 to afford a white glassy solid (69%): mp. 138-141°C;  $[\alpha]_{\text{D}}^{23}$  -105.5° (c  
15 0.5,  $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3375, 1787, 1659, 1515, 1421, 1278, 1256;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  9.32 (1H, m), 8.79 (1H, m), 8.47 (1H, m), 7.86-7.64 (4H, m), 5.31, 5.18, 4.59, 4.37 (4 or 5H, m), 3.55-2.76, 2.49-2.39, 2.05, 1.65 (11H, 4m). Anal. Calcd for  $\text{C}_{24}\text{H}_{25}\text{N}_5\text{O}_7 \cdot 1.5\text{H}_2\text{O}$ : C, 55.17; H, 5.40; N, 13.40. Found: C, 54.87; H, 5.22; N, 13.15.  
20 MS ( $\text{ES}^+$ , m/z) 494 ( $\text{M}^+ - 1$ , 100%).

- [3S(1S,9S)] t-Butyl 3-[6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-9-(thiophene-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-carbonylamino]-1-  
25 carboxamido]-4-oxobutanoate semicarbazone (502y), was synthesized via methods used to prepare 604 from 603 to afford a pale cream powder: mp. 120-180°C;  $[\alpha]_{\text{D}}^{23}$  -109° (c 0.18,  $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3478, 3327, 1670, 1582, 1543, 1421, 1279, 1257, 1155;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ,  $\text{CD}_3\text{OD}$ )  $\delta$   
30 8.04 (1H, m), 7.49 (1H, m), 7.38 (1H, m), 7.17 (1H, m),

- 584 -

5.17-5.01 (2H, m), 4.86 (1H, m), 4.61-4.50 (1H, m),  
 3.45-3.29 (2H, m), 3.21-3.03 (1H, m), 2.79-2.54 (3H,  
 m), 2.43-2.33 (1H, m), 2.11-1.66 (5H, m), 1.44 (9H, s).  
 Anal. Calcd for  $C_{24}H_{33}N_7O_7S \cdot H_2O$ : C, 49.56; H, 6.07; N,  
 5 16.86; S, 5.51. Found: C, 49.51; H, 5.93; N, 16.31; S,  
 5.17. MS ( $ES^+$ ) 586 (100%), 564 ( $M^+ + 1$ , 1.59).  
 Accurate mass calculated for  $C_{24}H_{34}N_7O_7S$  ( $MH^+$ ):  
 564.2240. Found: 564.2267.

[3*S*(1*S*,9*S*)] *t*-Butyl 3-[6,10-dioxo-9-(isoquinolin-1-  
 10 oylamino)-1,2,3,4,7,8,9,10-octahydro-6*H*-  
 pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido]-4-  
 oxobutanoate semicarbazone (502*z*), was prepared by a  
 similar method to that described for compound 604 to  
 afford a pale yellow solid (90%): mp. 142-145°C;  $[\alpha]_D^{24}$   
 15 -136.5° (c 0.06,  $CH_2Cl_2$ );  $^1H$  NMR ( $CDCl_3$ ) 8.951-9.46 (1*H*,  
 m), 9.11 (1*H*, s), 8.83 (1*H*, d, *J* = 7.8), 8.53 (1*H*, d, *J*  
 = 5.5), 7.89-7.83 (2*H*, m), 7.77-7.65 (2*H*, m), 7.55 (1*H*,  
 d, *J* = 7.2), 7.16 (1*H*, d, *J* = 2.7), 5.26-5.12 (2*H*, m),  
 4.87 (1*H*, m), 4.59 (1*H*, m), 3.25-3.12 (2*H*, m), 2.95-  
 20 2.76 (2*H*, m), 2.59-2.38, 2.18-1.94, 1.70 (5*H*, 3*m*), 1.44  
 (9*H*, s).



| compound | $R^4$ | $R^1$ |
|----------|-------|-------|
| 415a     |       |       |



- 585 -

| compound | R <sup>4</sup> | R <sup>1</sup> |
|----------|----------------|----------------|
| 415b     |                |                |
| 415c     |                |                |
| 214w-1   |                |                |
| 214w-2   |                |                |
| 214w-3   |                |                |
| 214w-4   |                |                |
| 214w-5   |                |                |
| 214w-6   |                |                |
| 214w-7   |                |                |
| 412g     |                |                |

5

10

- 586 -

| compound | R <sup>4</sup>  | R <sup>1</sup>  |
|----------|---|---|
| 412h     |  |  |

[1*S*,9*S*(2*S*,3*S*)] N-(2-Benzoyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (415a) was synthesized via methods used to prepare 550q to afford 415a.

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Ethoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(methylenedioxy benzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (415b) was synthesized via methods used to prepare 550q to afford 415b.

[1*S*,9*S*(2*R*,3*S*)] N-(2-Benzoyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(methylenedioxy benzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (415c) was synthesized via methods used to prepare 550q to afford 415c.

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Benzoyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(3,5-dimethyl-4-hydroxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (214w : ) was synthesized via methods used to prepare 550q to afford 214w-1.

[1*S*,9*S*(2*R*,3*S*)] N-(2-Benzoyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(3,5-dimethyl-4-hydroxybenzoylamino)-



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1,2,3,4,7,8,9,10-octahydro-6-H-  
pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (214w-2)  
was synthesized via methods used to prepare 550q to  
afford 214w-2.

- 5 [1*S*,9*S*(2*S*,3*S*)] N-(2-Benzoyloxy-5-oxotetrahydrofuran-3-  
yl)-6,10-dioxo-9-(3,5-dimethyl-4-hydroxybenzoylamino)-  
1,2,3,4,7,8,9,10-octahydro-6-H-  
pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (214w-3)  
was synthesized via methods used to prepare 550q to  
10 afford 214w-3.

- [1*S*,9*S*(2*R*,3*S*)] N-(2-Phenethoxy-5-oxotetrahydrofuran-3-  
yl)-6,10-dioxo-9-(3,5-dimethyl-4-hydroxybenzoylamino)-  
1,2,3,4,7,8,9,10-octahydro-6-H-  
pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (214w-4)  
15 was synthesized via methods used to prepare 550q to  
afford 214w-4.

- [1*S*,9*S*(2*S*,3*S*)] N-(2-Phenethoxy-5-oxotetrahydrofuran-3-  
yl)-6,10-dioxo-9-(3,5-dimethyl-4-hydroxybenzoylamino)-  
1,2,3,4,7,8,9,10-octahydro-6-H-  
20 pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (214w-5)  
was synthesized via methods used to prepare 550q to  
afford 214w-5.

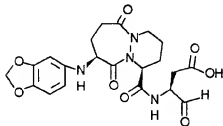
- [1*S*,9*S*(2*R*,3*S*)] N-(2-Cyclopentoxo-5-oxotetrahydrofuran-  
3-yl)-6,10-dioxo-9-(3,5-dimethyl-4-  
25 hydroxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-  
pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (214w-6)  
was synthesized via methods used to prepare 550q to  
afford 214w-6.

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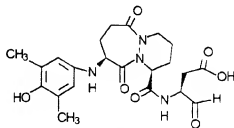
[1*S*,9*S*(2*S*,3*S*)] N-(2-Cyclopentoxo-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(3,5-dimethyl-4-hydroxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (214w-7) was synthesized via methods used to prepare 550q to afford 214w-7.

[1*S*,9*S*(2*R*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (412g) was synthesized via methods used to prepare 550q to afford 412g.

[1*S*,9*S*(2*S*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (412h) was synthesized via methods used to prepare 550q to afford 412h.



415

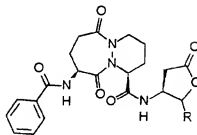


214w

[3*S*(1*S*,9*S*)] 3-(9-(4,5-Methylenedioxybenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (415), was synthesized by the method used to prepare 2002 from 2001 to afford 415.

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[3*S*(1*S*,9*S*)]3-(9-(3,5-Dichloro-4-hydroxybenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (214*w*), was synthesized by the method used to prepare 2002 from 2001 to afford 214*w*.



2100k-o

| compound | R |
|----------|---|
| 2100k    |   |
| 2100l    |   |
| 2100m    |   |
| 2100n    |   |
| 2100o    |   |

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- [1*S*,9*S*(2*RS*,3*S*)] 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-phenethyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (2100k),
- 5 was prepared by a similar method as compound 213e to afford a mixture of diastereoisomers (75/25) as a white solid (258mg, 83%): mp. 101°C;  $[\alpha]_D^{25}$  -96° (c 0.2, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3328, 2935, 2978, 1732, 1669, 1603, 1483, 1450, 1414, 1237, 1155, 1082, 989, 755; <sup>1</sup>H NMR
- 10 (CDCl<sub>3</sub>) δ 7.84-7.80 (2H, m), 7.54-7.17 (8H, m), 7.06-6.99 (1H, m), 6.25 (1H, d, J = 7.9H), 5.41 (0.75H, d, J = 5.4H), 5.31 (0.25H, bs), 5.23-5.09 (1H, m), 4.93-4.87 (1H, m), 4.68-4.51 (2H, m), 4.40-4.33 (0.25H, m), 4.24-4.14 (0.75H, m), 3.95-3.70 (1H, m), 3.30-3.13 (1H, m),
- 15 3.14-2.78 (5H, m), 2.47-2.21 (2H, m), 2.05-1.50 (5H, m). Anal. Calcd for C<sub>29</sub>H<sub>32</sub>N<sub>4</sub>O<sub>7</sub>•0.5H<sub>2</sub>O: C, 62.47; H, 5.97; N, 10.05. Found: C, 62.17; H, 5.83; N, 9.97. MS (ES<sup>+</sup>) 549.

- [1*S*,9*S*(2*RS*,3*S*)] 9-Benzamido-N-(2-cyclopentyloxy-5-oxo-tetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (2100l), was prepared by a similar method as 213e, (74%) as a colourless solid: mp. 172-80°C;  $[\alpha]_D^{23}$  -91.5° (c 0.1, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3290, 1792,
- 25 1677, 1657, 1642, 1544, 1425, 1280, 1259, 1124, 977; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.80 (2H, m), 7.46 (3.5H, m), 7.00 (1H, d, J = 6.7), 6.46 (0.5H, d, J = 7.9), 5.55 (0.5H, d, J = 5.3), 5.19 (2H, s + m), 4.93 (0.5H, m), 4.62 (1.5H, m), 4.34 (1H, m), 4.16 (0.5H, m), 3.28-2.70 (4H, m), 2.49-
- 30 2.29 (2H, m), 2.05-1.48 (15H, m).

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[1*S*,9*S*(2*R*,3*S*)] 9-Benzamido-6,10-dioxo-N-[2-(2-indanyloxy)-5-oxo-tetrahydrofuran-3-yl]-1,2,3,4,7,8,9,10-octahydro-6H-

pyridazino[1,2-a][1,2]diazepine-1-carboxamide (2100m),

- 5 was prepared by a similar method as 213e, (76%) as a colourless solid: mp. ~140°C, remelts 187-9°C;  $[\alpha]_D^{23}$  -96.9° (c 0.11, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3507, 3308, 3251, 1772, 1660, 1641, 1566, 1545, 1457, 1424, 1346, 1326, 1302, 1275, 1258, 1136, 1085, 1018, 981; <sup>1</sup>H NMR (CDCl<sub>3</sub>)
- 10 δ 7.78 (2H, m), 7.53 (3H, m), 7.19 (4H, m), 6.91 (1H, d, J = 7.4), 6.27 (1H, d, J = 7.6), 5.66 (1H, d, J = 5.3), 5.10 (1H, m), 4.96 (1H, m), 4.75 (2H, m), 4.52 (1H, m), 3.08 (3H, m), 3.03-2.71 (5H, m), 2.48-2.31 (2H, m), 1.90-1.40 (4H, m), 1.22 (1H, m).

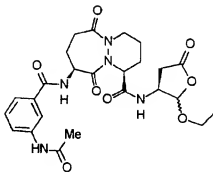
15 [1*S*,9*S*(2*S*,3*S*)] 9-Benzoylamino-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-

carboxamide (2100n), was prepared by a similar method to that described for compound 213e to afford a white

- 20 glassy solid (76%): mp. 112-5°C;  $[\alpha]_D^{23}$  -62.0° (c 0.1, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3305, 1789, 1677, 1665, 1535, 1422, 1279, 1256, 1119, 942, 700; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.84 (2H, m), 7.58-7.27 (9H, m), 6.99 (1H, d, J = 7.8), 5.23 (1H, s), 5.23-5.11 (1H, m), 4.89 (1H, m), 4.76 (1H, d, J =
- 25 11.3), 4.55 (1H, d, J = 11.4), 4.56-4.43 (2H, m), 3.30-2.96, 2.81-2.69, 2.46-2.37, 2.16-1.66 (10H, 4m), 2.27 (1H, d, J = 17.8). Anal. Calcd for C<sub>28</sub>H<sub>30</sub>N<sub>4</sub>O<sub>7</sub>·0.5H<sub>2</sub>O: C, 61.87; H, 5.75; N, 10.32. Found: C, 61.88; H, 5.70; N, 10.33. MS (ES<sup>+</sup>, m/z) 535 (M<sup>+</sup> + 1, 100%).

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- [1*S*,9*S*(2*R*,3*S*)] 9-Benzoylamino-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (2100o), (containing about 7% of (2*S*)), was prepared by a similar method to that described for compound 213e to afford a white glassy solid (81%): mp. 115-7°C;  $[\alpha]_D^{23}$  -121.8° (c 0.11, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3326, 1792, 1659, 1535, 1421, 1278, 1257, 1124, 978; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.82 (2H, m), 7.58-7.24 (8H, m), 6.90 (1H, d, J = 7.3), 6.49 (1H, d, J = 7.7), 5.57 (1H, d, J = 5.5), 5.11 (2H, m), 4.91 (1H, d, J = 11.4), 4.57 (1H, d, J = 11.1), 4.81-4.68 (1H, m), 4.65-4.54 (1H, m), 3.18-2.71 2.52-2.30, 2.05-1.62 (11H, 3m). Anal. Calcd for C<sub>28</sub>H<sub>30</sub>N<sub>4</sub>O<sub>7</sub>•0.5H<sub>2</sub>O: C, 61.87; H, 5.75; N, 10.32. Found: C, 61.70; H, 5.71; N, 10.15. MS (ES<sup>+</sup>, m/z) 535 (M<sup>+</sup> + 1, 94.3%), 557 (100%).

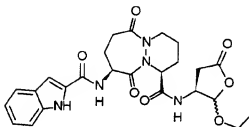


550n

- [1*S*,9*S*(2*R*,3*S*)] 9-(3-Acetamido)benzoylamino-6,10-dioxo-N-(2-ethoxy-5-oxo-tetrahydrofuran-3-yl)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550n), was prepared by a similar method as compound 213e to

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afford a mixture of diastereoisomers (65/35) as a tan powder (390mg, 28%): mp. 139-145°C;  $[\alpha]_D^{23}$  -104° (c 0.2, MeOH); IR (KBr) 3318, 2405, 2369, 1792, 1660, 1591, 1549, 1484, 1422, 1257, 1117;  $^1\text{H}$  NMR ( $\text{D}_6$ -DMSO)  $\delta$  10.1 (1H, s), 8.80 (0.65H, d,  $J$  = 6.6), 8.58 (0.35H, d,  $J$  = 6.6), 8.59 (1H, d,  $J$  = 7.0), 8.06 (1H, bs), 7.83-7.79 (1H, m), 7.61-7.57 (1H, m), 7.47-7.39 (1H, m), 5.61 (0.35H, d,  $J$  = 5.0), 5.37 (0.65H, bs), 5.17-5.14 (0.35H, m), 5.08-5.06 (0.65H, m), 4.92-4.86 (1H, m), 4.67-4.61 (0.35H, m), 4.47-4.41 (0.65H, m), 4.26-4.11 (1H, 2m), 3.80-3.59 (2H, m), 3.23-2.75 (3H, m), 2.61-1.48 (7H, m), 2.10 (3H, s), 1.25 and 1.17 (3H, 2t,  $J$  = 5.8). MS ( $\text{ES}^+$ ) 528.

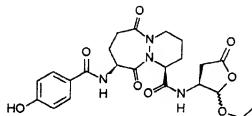


550o

15 [1*S*, 9*S*(2*RS*, 3*S*)] 6,10-Dioxo-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-9-(2-indoloylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550o), was synthesized by a similar method as compound 213e to afford a colourless solid (1.071g, 80%): mp. 155-70°C;  $[\alpha]_D^{22}$  -75.8° (c 0.26,  $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3314, 2941, 1791, 1658, 1545, 1420, 1341, 1312, 1252, 1181, 1118, 939, 749;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  9.45 (0.5H, s), 9.34 (0.5H, s), 7.68-7.62 (1H, m), 7.49-7.39 (2H, m), 7.33-7.26

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(1H, m), 7.18-7.03 (3H, m), 5.49 (0.5H, d), 5.30 (0.5H, s), 5.26-5.13 (1H, m), 4.90-4.83 (0.5H, m), 4.76-4.49 (1H, m), 4.42-4.35 (0.5H, m), 3.97-3.74 (1H, m), 3.72-3.53 (1H, m), 3.35-2.64 (4H, m), 2.50-2.37 (1H, m), 2.20-1.82 (5H, m), 1.69-1.50 (2H, m), 1.30-1.19 (3H, m).

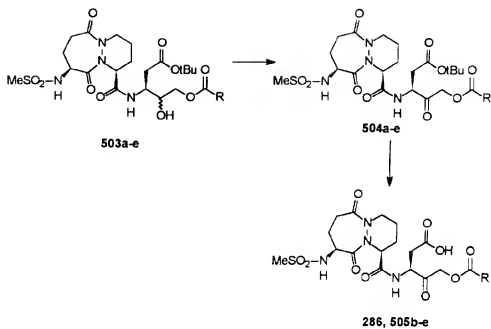






550p

[1S,9S(2RS,3S)] 6,10-Dioxo-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-9-(4-hydroxybenzoyl)amino-  
 10 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550p),  
 was prepared by a similar method as compound 213e to afford a mixture of diastereoisomers as a white foam (820mg, 47%):  $[\alpha]_D^{24}$  -75° (c 0.16, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr)  
 15 3401, 2937, 1791, 1657, 1609, 1539, 1505, 1423, 1277, 1177, 1118; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.07-8.05 (1H, m), 7.67 (2H, d, J = 7.9), 7.38-7.29 (2H, m), 6.80 (2H, d, J = 8.5), 5.49 (0.5H, d, J = 4.6), 5.23 (0.5H, bs), 5.24-5.20 (1H, m), 5.12-5.08 (1H, m), 4.68-4.29 (2H, m), 3.92-  
 20 3.45 (3H, m), 3.32-2.30 (2H, m), 2.80-1.56 (11H, m), 1.21 (3H, t, J = 7.0H).

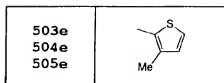


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| compound             | R   |
|----------------------|---|
| 503a<br>504a<br>286  |    |
| 503b<br>504b<br>505b |    |
| 503c<br>504c<br>505c |   |
| 503d<br>504d<br>505d |  |

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- [3*S*,4*R*(1*S*,9*S*)] *t*-Butyl 3-(6,10-dioxo-9-methanesulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-4-hydroxy-5-(1-naphthoyloxy)pentanoate (503a), was prepared from 212b and (3*S*,4*R*) *t*-butyl (N-allyloxycarbonyl)-3-amino-4-hydroxy-5-(1-naphthoyloxy)pentanoate by the method described for (213e) to afford 533mg (81%) of an off-white foam:  $[\alpha]_D^{22}$  -81.4° (c 0.5, CH<sub>2</sub>Cl<sub>2</sub>); IR(KBr) 3342, 2976, 1719, 1664, 1328, 1278, 1246, 1153, 1137. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.86 (1H, d, J = 8.4), 8.21 (1H, dd, J = 1.3, 7.3), 8.03 (1H, d, J = 8.1), 7.88 (1H, d, J = 8.6), 7.66-7.45 (3H, m), 7.23 (1H, d, J = 8.6), 5.96 (1H, d, J = 9.2), 5.30 (1H, m), 4.59-4.33 (5H, m), 4.24 (1H, m), 3.96 (1H, brd), 3.29 (1H, m), 2.95 (1H, m), 2.93 (3H, s), 2.69-2.50 (3H, m), 2.36 (1H, m), 1.96 (4H, m), 1.62 (1H, m), 1.41 (9H, s). Anal. Calcd for C<sub>31</sub>H<sub>40</sub>N<sub>4</sub>O<sub>10</sub>S•0.25H<sub>2</sub>O : C, 55.97; H, 6.14; N, 8.42. Found: C, 55.90; H, 6.11; N, 8.23. M.S. (ES<sup>+</sup>) 683 (M+Na, 100%), 661 (M+1,39), 605 (78).

- [3*S*(1*S*,9*S*)] *t*-Butyl 3-(6,10-dioxo-9-methanesulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-5-(1-naphthoyloxy)-4-oxopentanoate (504a), was synthesized from 503a via method used to prepare 216e from 215e to afford 446mg (91%) of a colourless foam:  $[\alpha]_D^{21}$  -111.6°

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- (c 0.5, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3319, 2978, 2936, 1723, 1670, 1413, 1370, 1329, 1278, 1246, 1153. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.87 (1H, d, J = 8.9), 8.29 (1H, d, J = 7.2), 8.06 (1H, d, J = 8.3), 7.90 (1H, d, J = 8.2), 7.66-7.48 (3H, m), 7.37 (1H, d, J = 8.1), 5.61 (1H, d, J = 9.0), 5.31 (1H, m), 5.22 (1H, AB, J = 16.9), 5.09 (1H, AB, J = 16.92), 4.99 (1H, m), 4.65-4.43 (2H, m), 3.28 (1H, m), 2.96 (3H, s), 2.86 (2H, m), 2.59 (1H, m), 2.38 (1H, dd, J = 6.8, 13.2), 2.21-1.70 (6H, m), 1.45 (9H, s). Anal.
- 10 Calcd for C<sub>31</sub>H<sub>38</sub>N<sub>4</sub>O<sub>10</sub>S•0.25H<sub>2</sub>O. C, 56.14; H, 5.85; N, 8.45. Found: C, 56.11; H, 5.83; N, 8.29. M.S. (ES<sup>+</sup>) 657 (M-1, 100%).

[3S(1S,9S)] 3-(6,10-Dioxo-9-methanesulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-

- 15 pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-5-(1-naphthoxyloxy)-4-oxopentanoic acid (286), was prepared from 504a by the method described for 217 to afford 356mg (93%) of a white powder: mp 120-123°C; [α]<sub>D</sub><sup>23</sup> -121° (c 0.194, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3314, 2937, 1722,
- 20 1663, 1412, 1328, 1278, 1245, 1195, 1132. <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ 12.63 (1H, brs), 8.94 (1H, d, J = 7.4), 8.78 (1H, d, J = 8.6), 8.26 (2H, m), 8.11 (1H, d, J = 8.0), 7.77-7.62 (4H, m), 5.28 (2H, s), 5.21 (1H, m), 4.82 (1H, m), 4.44-4.29 (2H, m), 3.31 (1H, m), 2.98 (3H, s), 2.98-
- 25 2.86 (2H, m), 2.72 (1H, dd, J = 7.3, 16.9), 2.40 (1H, m), 2.24-1.84 (4H, m), 1.69 (2H, m). Anal. Calcd for C<sub>27</sub>H<sub>30</sub>N<sub>4</sub>O<sub>10</sub>S•H<sub>2</sub>O : C, 52.25; H, 5.20; N, 9.03. Found: C, 52.11; H, 4.97; N, 8.89. M.S. (ES<sup>+</sup>) 601 (M-1, 100%).

- 30 [3S,4RS(1S,9S)] t-Butyl 3-[6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-9-

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- (methanesulphonylamino)-1-carboxamido]-4-hydroxy-5-(5-methyl-3-phenylisoxazoyloxy)pentanoate (503b), was synthesized by a similar method as compound 213e, to afford an off-white powder (671mg, 88%): mp. 90-120°C;
- 5 IR (KBr) 3345, 2977, 1727, 1664, 1532, 1450, 1423, 1369, 1323, 1310, 1276, 1257, 1154, 1101, 990, 766; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.61-7.55 (2H, m), 7.51-7.42 (3H, m), 6.86 (1H, d), 5.69 (1H, d), 5.21 (1H, m), 4.64-4.38 (2H, m), 4.15-4.05 (3H, m), 3.84 (1H, s), 3.31-3.14 (2H, m),
- 10 2.97-2.87 (1H, m), 2.94 (3H, s), 2.76 (3H, s), 2.64-2.48 (3H, m), 2.39-2.29 (1H, m), 2.04-1.61 (5H, m). Anal. Calcd for C<sub>31</sub>H<sub>41</sub>N<sub>5</sub>O<sub>11</sub>S•H<sub>2</sub>O: C, 52.46; H, 6.11; N, 9.87; S, 4.52. Found: C, 52.34; H, 5.92; N, 9.56; S, 4.44. MS (ES<sup>+</sup>) 714 (47%), 692 (M<sup>+</sup> + 1, 84), 636 (100).
- 15 [3S(1S,9S)] t-Butyl 3-[6,10-dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-5-(5-methyl-3-phenylisoxazoyloxy)-4-oxopentanoate (504b), was synthesized by a similar method as compound 216b to
- 20 afford a colourless powder (601mg, 93%): mp. 75-115°C; [α]<sub>D</sub><sup>23</sup> -104° (c 0.26, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3324, 2977, 2935, 1730, 1670, 1525, 1452, 1422, 1369, 1317, 1276, 1256, 1222, 1155, 1107, 990, 766; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.68-7.61 (2H, m), 7.47-7.38 (3H, m), 7.32-7.24 (1H, m),
- 25 5.56 (1H, d), 5.36-5.24 (1H, m), 5.04 (1H, d), 4.86 (1H, d), 4.86-4.77 (1H, m), 4.64-4.39 (2H, m), 3.32-3.17 (1H, m), 2.97-2.85 (1H, m), 2.93 (3H, s), 2.76 (3H, s), 2.80-2.71 (1H, m), 2.65-2.49 (1H, m), 2.41-2.30 (1H, m), 2.12-1.61 (6H, m), 1.42 (9H, s). Anal.
- 30 Calcd for C<sub>31</sub>H<sub>39</sub>N<sub>5</sub>O<sub>11</sub>S•H<sub>2</sub>O: C, 52.61; H, 5.84; N, 9.90; S, 4.53. Found: C, 52.94; H, 5.69; N, 9.72; S, 4.51.

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MS ( $\text{ES}^+$ ) 712 (31%), 707 (100), 690 ( $\text{M}^+ + 1$ , 41), 634 (55).

[3S(1S,9S)] 3-[6,10-Dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-

- 5 pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-5-(5-methyl-3-phenylisoxazoyloxy)-4-oxopentanoic acid (505b), was synthesized by a similar method as compound 217 to afford a colourless powder (499mg, 96%): mp. 95-145°C;  $[\alpha]_{\text{D}}^{22}$  -137° (c 0.12, MeOH); IR (KBr) 3323, 2936, 1732, 1665, 1529, 1452, 1421, 1312, 1275, 1256, 1021, 1183, 1153, 1135, 1101, 990;  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.67-7.56 (2H, m), 7.49-7.38 (4H, m), 5.23-5.12 (1H, m), 5.02 (1H, d), 4.79-4.73 (1H, m), 4.52-4.34 (3H, m), 3.48-3.25 (2H, m), 3.03-2.85 (2H, m), 2.94 (3H, s), 2.74 (3H, s), 2.79-2.66 (1H, m), 2.52-2.38 (1H, m), 2.29-2.14 (1H, m), 2.04-1.70 (4H, m). Anal. Calcd for  $\text{C}_{27}\text{H}_{31}\text{N}_5\text{O}_{11}\text{S}\cdot\text{H}_2\text{O}$ : C, 49.77; H, 5.18; N, 10.75; S, 4.92. Found: C, 49.83; H, 5.01; N, 10.27; S, 4.84. MS ( $\text{ES}^+$ ) 746 (42%), 632 ( $\text{M} - 1$ , 100), 386 (60). Accurate mass 20 calculated for  $\text{C}_{27}\text{H}_{32}\text{N}_5\text{O}_{11}\text{S}$  ( $\text{MH}^+$ ): 634.1819. Found: 634.1807.

[3S,4RS(1S,9S)] t-Butyl 3-[6,10-dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-

- 25 hydroxy-5-(2-phenoxybenzoyloxy)pentanoate (503c), was synthesized by a similar method as compound 213e to afford a colourless solid (446mg, 84%): IR (KBr) 3345, 2976, 2935, 1727, 1664, 1603, 1535, 1483, 1451, 1416, 1395, 1369, 1328, 1297, 1277, 1237, 1155, 1135, 1076, 990, 755;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.98-7.89 (1H, m), 7.55-7.45

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(1H, m), 7.39-7.18 (3H, m), 7.14-7.07 (1H, m), 7.00-6.90 (3H, m), 6.75 (1H, d), 5.57-5.50 (1H, m), 5.21-5.09 (1H, m), 4.64-4.42 (2H, m), 4.36-4.12 (3H, m), 3.95-3.87 (1H, m), 3.39-3.18 (1H, m), 3.00-2.82 (1H, m), 2.95 (3H, s), 2.69-2.48 (3H, m), 2.42-2.28 (1H, m), 2.07-1.62 (6H, m), 1.42 (9H, s). Anal. Calcd for  $C_{33}H_{42}N_4O_{11}S \cdot H_2O$ : C, 54.99; H, 6.15; N, 7.77; S, 4.45. Found: C, 54.95; H, 5.95; N, 7.34; S, 4.20. MS ( $ES^+$ ) 725 (26%), 720 (47), 703 ( $M^+ + 1$ , 34), 433 (100), 403 (89).

[3S(1S,9S)] t-Butyl 3-[6,10-dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-(2-phenoxybenzoyloxy) pentanoate (504c), was synthesized by a similar method as compound 216e to afford a colourless powder: mp. 85-100°C;  $[\alpha]_D^{22}$  -91.3° (c 0.52,  $CH_2Cl_2$ ); IR (KBr) 3328, 2978, 2935, 1732, 1669, 1603, 1524, 1483, 1450, 1396, 1369, 1296, 1276, 1237, 1155, 1132, 1082, 989, 755;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  8.03-7.98 (1H, m), 7.52-7.44 (1H, m), 7.37-7.07 (5H, m), 7.01-6.92 (3H, m), 5.52 (1H, d), 5.28-5.20 (1H, m), 5.06-4.84 (3H, m), 4.64-4.39 (2H, m), 3.32-3.14 (1H, m), 2.99-2.88 (1H, m), 2.94 (3H, s), 2.65-2.45 (2H, m), 2.39-2.29 (1H, m), 2.12-1.58 (6H, m), 1.40 (9H, s). Anal. Calcd for  $C_{33}H_{40}N_4O_{11}S$ : C, 56.56; H, 5.75; N, 8.00; S, 4.58. Found: C, 56.37; H, 5.84; N, 7.69; S, 4.37. MS ( $ES^+$ ) 723 (30%), 718 (100), 701 ( $M^+ + 1$ , 23), 645 (59).

[3S(1S,9S)] 3-[6,10-Dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-

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- (2-phenoxybenzoyloxy)pentanoic acid (505c), was synthesized by a similar method as compound 217 to afford a colourless foam (252mg, 72%): mp. 90-125°C;  $[\alpha]_D^{23}$  -133° (c 0.11, MeOH); IR (KBr) 3314, 2938, 1792, 1734, 1663, 1604, 1535, 1483, 1448, 1415, 1250, 1132, 756;  $^1\text{H}$  NMR ( $\text{D}_6$ -DMSO)  $\delta$  8.81-8.76 (1H, m), 7.92 (1H, d), 7.68-7.54 (2H, m), 7.41-7.25 (3H, m), 7.16-6.91 (4H, m), 5.13-4.98 (2H, m), 4.72-4.63 (1H, m), 4.37-4.21 (2H, m), 2.92 (3H, s), 2.90-2.60 (3H, m), 2.35-2.26 (1H, m), 2.17-2.05 (2H, m), 1.99-1.80 (2H, m), 1.61-1.50 (1H, m). Anal. Calcd for  $\text{C}_{29}\text{H}_{32}\text{N}_4\text{O}_{11}\text{S} \cdot 0.5\text{H}_2\text{O}$ : C, 53.29; H, 5.09; N, 8.57; S, 4.90. Found: C, 53.57; H, 5.18; N, 8.32; S, 4.75. MS ( $\text{ES}^+$ ) 643 ( $\text{M} - 1$ , 100%).
- 15 [3S,4RS(1S,9S)] t-Butyl 3-[6,10-dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-hydroxy-5-(3-phenoxybenzoyloxy) pentanoate (503d), was synthesized by a similar method as compound 213e to afford a colourless solid (563mg, 90%): IR (KBr) 3349, 2978, 2935, 1724, 1664, 1583, 1536, 1489, 1443, 1370, 1327, 1271, 1226, 1189, 1155, 1073, 990, 755;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.77 (1H, d), 7.67 (1H, m), 7.45-7.10 (6H, m), 7.00 (2H, d), 5.93-5.80 (1H, m), 5.36-5.30 (1H, m), 4.63-4.24 (5H, m), 4.15-4.09 (1H, m), 3.37-3.22 (1H, m), 2.98-2.74 (1H, m), 2.94 (3H, s), 2.70-2.47 (3H, m), 2.40-2.30 (1H, m), 2.15-1.60 (5H, m), 1.42 (9H, s). Anal. Calcd for  $\text{C}_{33}\text{H}_{42}\text{N}_4\text{O}_{11}\text{S} \cdot \text{H}_2\text{O}$ : C, 54.99; H, 6.15; N, 7.77; S, 4.45. Found: C, 54.60; H, 5.88; N, 7.49; S, 4.50. MS ( $\text{ES}^+$ ) 725 (19%), 720 (91), 703 ( $\text{M}^+ + 1$ , 74), 647 (76), 629 (100), 433 (78).

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[3S(1S,9S)] t-Butyl 3-[6,10-dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-(3-phenoxybenzoyloxy) pentanoate (504d), was synthesized by a similar method as compound 216e to afford a colourless powder (466mg, 85%): mp. 75-100°C;  $[\alpha]_D^{22}$  -99.3° (c 0.60, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3335, 2978, 2937, 1728, 1669, 1584, 1525, 1487, 1444, 1416, 1369, 1328, 1272, 1227, 1188, 1155, 989, 754; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.82-7.77 (1H, m), 7.66-7.65 (1H, m), 7.46-7.32 (4H, m), 7.26-7.10 (2H, m), 7.04-6.98 (2H, m), 5.68 (1H, d), 5.37-5.31 (1H, m), 5.11 (1H, d), 5.02-4.88 (2H, m), 4.66-4.42 (2H, m), 3.35-3.17 (1H, m), 2.98-2.89 (1H, m), 2.96 (3H, s), 2.84-2.78 (1H, m), 2.72-2.47 (1H, m), 2.42-2.32 (1H, m), 2.14-1.58 (6H, m), 1.43 (9H, s). Anal. Calcd for C<sub>33</sub>H<sub>40</sub>N<sub>4</sub>O<sub>11</sub>S: C, 56.56; H, 5.75; N, 8.00. Found: C, 56.36; H, 5.82; N, 7.71. MS (ES<sup>+</sup>) 723 (56%), 718 (90), 701 (M<sup>+</sup> + 1, 36), 645 (100).

[3S(1S,9S)] 3-[6,10-Dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-(3-phenoxybenzoyloxy)pentanoic acid (505d), was synthesized by a similar method as compound 217 to afford a colourless foam (353mg, 73%): mp. 80-115°C;  $[\alpha]_D^{23}$  -138° (c 0.11, MeOH); IR (KBr) 3327, 2937, 1728, 1666, 1584, 1529, 1487, 1443, 1413, 1328, 1273, 1227, 1189, 1155, 1134, 989, 754; <sup>1</sup>H NMR (D<sub>6</sub>-DMSO) δ 8.82 (1H, d), 7.76-7.72 (1H, m), 7.61-7.53 (2H, m), 7.48-7.32 (4H, m), 7.24-7.17 (1H, m), 7.11-7.06 (2H, m), 5.14-5.06 (3H, m), 4.73-4.64 (1H, m), 4.38-4.24 (2H, m), 2.92 (3H, s), 2.89-2.61 (3H, m), 2.38-2.27 (1H, m),



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2.19-2.06 (2H, m), 2.02-1.79 (3H, m), 1.63-1.52 (1H, m). Anal. Calcd for  $C_{29}H_{32}N_4O_{11}S \cdot 0.5H_2O$ : C, 53.29; H, 5.09; N, 8.57; S, 4.90. Found: C, 53.24; H, 5.14; N, 8.34; S, 4.86. MS ( $ES^+$ ) 643 (M - 1, 100%), 385 (62).

- 5 [3S,4R(1S,9S)] t-Butyl 5-(3-chlorothien-2-oyloxy)-3-(6,10-dioxo-9-methanesulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-hydroxypentanoate (503e), was prepared by a similar method to that described for compound
- 10 213e, to afford an off white solid (70%): mp. 100-103°C;  $[\alpha]_D^{25}$  -84.0° (c 0.05,  $CH_2Cl_2$ ); IR (KBr) 3459-3359, 1722, 1664, 1514, 1368, 1328, 1278, 1247, 1155;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.52 (1H, m), 7.06-6.99 (2H, m), 5.69 (1H, d, J = 9.0), 5.23 (1H, m), 4.61-4.16 (6H, m),
- 15 3.36-3.19 (1H, m), 2.96 (3H, s), 2.67-2.49, 2.42-2.32, 2.06-1.89, 1.69 (10H, 4m), 1.43 (9H, s).

- [3S(1S,9S)] t-Butyl 5-(3-chlorothien-2-oyloxy)-3-(6,10-dioxo-9-methanesulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxopentanoate (504e), was prepared by a
- 20 similar method to that described for compound 216e, to afford a white solid (98%): mp. 91-98°C;  $[\alpha]_D^{25}$  -112.5° (c 0.06,  $CH_2Cl_2$ ); IR (KBr) 3453-3364, 1727, 1668, 1513, 1420, 1368, 1245, 1155;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.54
- 25 (1H, d, J = 5.3), 7.18 (1H, d, J = 7.18), 7.05 (1H, d, J = 5.4), 5.42 (1H, d, J = 8.9), 5.25 (1H, m), 5.02 (2H, m), 4.96-4.87 (1H, m), 4.65-4.42 (2H, m), 3.34-3.17 (1H, m), 2.97-2.93 (1H, m), 2.97 (3H, s), 2.87-2.78, 2.73-2.50, 2.38-2.32, 2.13-1.88, 1.69-1.60 (9H,
- 30 5m), 1.44 (9H, s).

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[3S(1S,9S)] 5-(3-Chlorothiien-2-oyloxy)-3-(6,10-dioxo-9-methanesulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxopentanoic acid (505e). A solution of 217 (0.33g,

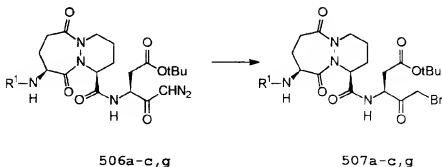
5 0.51mmol) in dry dichloromethane (3ml) was cooled (ice/water) with protection from moisture.

Trifluoroacetic acid (2ml) was added with stirring. The solution was kept at room temperature for 2h after removal of the cooling bath, then concentrated in

10 vacuo. The residue was evaporated three times from dichloromethane, triturated with diethyl ether and filtered. The solid was purified by flash

chromatography (silica gel, 0-6% methanol in dichloromethane) to give the product as a white glassy

15 solid (0.296g, 98%): mp 110-122°C;  $[\alpha]_D^{22}$  -163.5° (c 0.1, CH<sub>3</sub>OH); IR (KBr) 3514-3337, 1726, 1664, 1513, 1420, 1245, 1152, 1134, 990; <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.79 (1H, d, J = 5.2), 7.12 (1H, d, J = 5.2), 5.20 (1H, m), 5.02-4.72 (2H, m, masked by H<sub>2</sub>O), 4.59-4.32 (3H, m), 3.48-3.29, 3.08-2.75, 2.50-2.41, 2.31-2.22, 2.08-1.89, 1.72-1.63 (11H, 6m), 2.95 (3H, s).



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| compound | R <sup>1</sup>        |
|----------|-----------------------|
| 506a     | PhC(O)-               |
| 507a     |                       |
| 506b     | MeS(O) <sub>2</sub> - |
| 507b     |                       |
| 506c     | MeOC(O)-              |
| 507c     |                       |
| 506g     | CH <sub>3</sub> C(O)- |
| 507g     |                       |

- 5
- 10 [3*S*(1*S*,9*S*)] *t*-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-5-diazo-4-oxopentanoate (506a). A solution of 212e (321mg, 0.929mmol) and (3*S*) *t*-butyl 3-amino-5-diazo-4-
- 15 oxopentanoate (198mg, 0.929mmol) in dichloromethane (3ml) was cooled to 0° and *N,N*-diisopropylethylamine (0.16ml, 1.86mmol) and [2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyl-uronium tetrafluoroborate (328mg, 1.02mmol) were added. The solution was stirred
- 20 overnight at room temperature, diluted with ethyl acetate and washed with 1M NaHSO<sub>4</sub> (x2), aqueous NaHCO<sub>3</sub> (x2), brine, dried over magnesium sulphate and evaporated. Chromatography on silica gel eluting with ethyl acetate gave 506a (425mg, 85%) as a colourless
- 25 foam: [α]<sub>D</sub><sup>23</sup> -124.9° (c 0.2, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3332, 2111, 1728, 1658, 1532, 1421, 1392, 1367, 1279, 1256, 1155; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.82 (2*H*, m), 7.49 (3*H*, m), 7.28 (1*H*, d, *J* = 9.3), 7.05 (1*H*, d, *J* = 7.3), 5.06 (1*H*, s), 5.18 (2*H*, m), 4.78 (1*H*, m), 4.62 (1*H*, m), 3.29 (1*H*, m), 3.08-2.79 (3*H*, m), 2.58 (1*H*, dd, *J* = 16.8, 5.6), 2.20-
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1.85 (4H, m), 1.70 (1H, m), 1.45 (9H, s). MS ( $ES^+$ )  
539.58 (M - 1, 97.9%) 529.59 (100).

[3S(1S,9S)] t-Butyl 5-diazo-3-[6,10-dioxo-(9-methanesulphonamido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxopentanoate (506b), was prepared by a similar method as compound 506a. 74% as yellow orange solid: mp. 75°C (decomp.);  $[\alpha]_D^{20}$  -92.0° (c 0.036,  $CH_2Cl_2$ ); IR (KBr) 3438, 2904, 2113, 1728, 1669, 1523, 1368, 1328, 1155; <sup>1</sup>H NMR ( $CDCl_3$ )  $\delta$  7.48 (1H, d, J = 8.1), 5.83-5.68 (1H, m), 5.55-5.50 (1H, m), 5.43-5.14 (1H, m), 4.83-4.45 (3H, m), 3.40-3.19 (1H, m), 2.98 (3H, s), 2.92-2.30 (4H, m), 2.24-1.70 (6H, m), 1.43 (9H, s).

[3S(1S,9S)] t-Butyl 5-diazo-3-[6,10-dioxo-(9-methoxycarbonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxopentanoate (506c), was prepared by a similar method as compound 506a to afford a pale yellow foam (405mg, 82%);  $[\alpha]_D^{20}$  -144° (c 0.2,  $CH_2Cl_2$ ); IR (KBr) 3339, 2978, 2958, 2112, 1728, 1674, 1530, 1459, 1415, 1367, 1274, 1252, 1154, 1063; <sup>1</sup>H NMR ( $CDCl_3$ )  $\delta$  7.23 (1H, d, J = 8.2), 5.51-5.31 (2H, m), 5.21-5.16 (1H, m), 4.77-4.55 (3H, m), 3.68 (3H, s), 3.35-3.18 (1H, m), 3.04-2.51 (4H, m), 2.40-2.30 (1H, m), 2.09-1.66 (5H, m), 1.45 (9H, s). MS ( $ES^+$ ) 493.

[3S(1S,9S)] t-Butyl 3-(9-acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-5-diazo-4-oxopentanoate (506g), was prepared by a similar

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- method as compound **506a**. 81%:  $[\alpha]_D^{28} -146.7^\circ$  (c 0.4,  $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3438, 2904, 2113, 1728, 1669, 1523, 1368, 1328, 1155;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.32 (1H, d), 6.43 (1H, d), 5.50 (1H, s), 5.22 (1H, m), 4.94 (1H, m), 4.77 (1H, m), 4.60 (1H, m), 3.24 (1H, m), 3.03-2.52 (4H, m), 2.36 (1H, m), 2.10-1.64 (5H, m), 2.02 (3H, s), 1.45 (9H, s). Anal. Calcd for  $\text{C}_{21}\text{H}_{20}\text{N}_6\text{O}_7$ : C, 52.69; H, 6.32; N, 17.05. Found: C, 52.51; H, 6.27; N, 17.36. MS ( $\text{ES}^+$ ) 477 ( $\text{M}^+ - 1$ , 100%).
- 10 **[3S(1S,9S)] t-Butyl 5-bromo-3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxopentanoate (507a)**. **506a** (3.0g, 5.55mmol) in dry dichloromethane (40ml) was cooled to  $0^\circ$  and 30%
- 15 hydrobromic acid in acetic acid (1.1ml, 5.55mmol) was added dropwise over 4min. The mixture was stirred at  $0^\circ$  for 9min and quenched with aqueous sodium bicarbonate. The product was extracted into ethyl acetate, washed with aqueous sodium bicarbonate, brine,
- 20 dried ( $\text{MgSO}_4$ ) and evaporated to give 2.97g (92%) of a colourless foam:  $[\alpha]_D^{23} -82.3^\circ$  (c 0.23,  $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3333, 1726, 1659, 1530, 1458, 1447, 1422, 1395, 1368, 1279, 1256, 1222, 1155, 728;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.81 (2H, m), 7.50 (3H, m), 7.11 (1H, d,  $J = 8.0$ ), 7.01 (1H, d,  $J = 7.4$ ), 5.20 (2H, m), 5.00 (1H, m), 4.06 (2H, s), 3.28 (1H, m), 3.20-2.70 (4H, m), 2.42 (1H, m), 2.10-1.85 (4H, m), 1.72 (1H, m), 1.44 (9H, s). Anal. Calcd for  $\text{C}_{26}\text{H}_{33}\text{N}_4\text{O}_7\text{Br} \cdot \text{C} \cdot 0.7\text{H}_2\text{O}$ : C, 51.53; H, 5.72; N, 9.24. Found: C, 51.55; H, 5.52; N, 9.09. MS ( $\text{ES}^+$ ) 593, 593 ( $\text{M}^+ + 1$ ).

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[3S(1S,9S)] t-Butyl 5-bromo-3-(6,10-dioxo-9-methanesulphonamido-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxopentanoate (507b), was prepared by a similar method

- 5 as compound 507a. (68%) as an orange foam:  $[\alpha]_D^{20}$  -135° (c 0.053, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3429, 2944, 2935, 1723, 1670, 1458, 1408, 1327, 1225, 1154, 991; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.38 (1H, d, J = 8.2), 5.69 (1H, d, J = 9.3), 5.43-5.34 (1H, m), 5.07-4.97 (1H, m), 4.70-4.42 (2H, m), 4.12 (2H, s), 3.35-3.17 (1H, m), 3.10-2.69 (4H, m), 2.98 (3H, s), 2.43-2.33 (1H, m), 2.15-1.65 (5H, m), 1.43 (9H, s). Anal. Calcd for C<sub>20</sub>H<sub>31</sub>BrN<sub>4</sub>O<sub>8</sub>S: C, 42.33; H, 5.51; N, 9.87. Found: C, 42.69; H, 5.52; N, 9.97.

[3S(1S,9S)] t-Butyl 5-bromo-3-(6,10-dioxo-9-

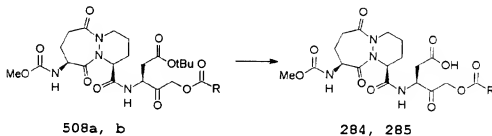
- 15 (methoxycarbonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxopentanoate (507c), was prepared by a similar method as compound 507a to afford a pale yellow foam (320mg, 78%):  $[\alpha]_D^{20}$  -107° (c 0.2, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3401, 2956, 1726, 1670, 1528, 1452, 1415, 1395, 1368, 1276, 1251, 1155, 1064; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.07 (1H, d, J = 7.6), 5.47 (1H, d, J = 8.1), 5.21-5.16 (1H, m), 5.03-4.94 (1H, m), 4.75-4.56 (2H, m), 4.06 (2H, s), 3.69 (3H, s), 3.31-3.13 (1H, m), 3.03-2.92 (2H, m), 2.81-2.58 (2H, m), 2.41-2.31 (1H, m), 2.10-1.66 (5H, m), 1.44 (9H, s).

[3S(1S,9S)] t-Butyl 3-(9-acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-5-bromo-4-oxopentanoate (507g), was prepared by a similar

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method as compound **507a** to afford a pale yellow foam (84%):  $[\alpha]_D^{22}$  -109.6° (c 0.1, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3324, 1727, 1659, 1535, 1458, 1444, 1423, 1369, 1279, 1256, 1223, 1155; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.12 (1H, d, J = 7.8), 6.33 (1H, d, J = 7.5), 5.19 (1H, m), 4.97 (2H, m), 4.58 (1H, m), 4.06 (2H, s), 3.20 (1H, m), 3.05-2.69 (4H, m), 2.35 (1H, m), 2.14-1.68 (5H, m), 2.03 (3H, s), 1.44 (9H, s). Anal. Calcd for C<sub>21</sub>H<sub>31</sub>BrN<sub>4</sub>O<sub>7</sub>·0.3H<sub>2</sub>O: C, 46.99; H, 5.93; N, 10.44. Found: C, 46.97; H, 5.90; N, 10.35.



10

| compound                  | R |
|---------------------------|---|
| <b>508a</b><br><b>284</b> |   |
| <b>508b</b><br><b>285</b> |   |

15 [3*S*(1*S*,9*S*)] *t*-Butyl 5-(2,6-dichlorobenzoyloxy)-3-[6,10-dioxo-9-(methoxycarbonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoate (**508a**). To a solution of

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- 506c (547mg, 1mmol) in DMF (4ml) was added potassium fluoride (145mg, 2.5mmol, 2.5 equiv). After 10min stirring at room temperature, 2,6-dichlorobenzoic acid (229mg, 1.2mmol, 1.2 equiv) was added. After 3h reaction at room temperature, ethyl acetate (30ml) was added. The solution was washed with a saturated solution of sodium bicarbonate (30ml), brine, dried over  $\text{MgSO}_4$  and concentrated in vacuo to afford 590mg (90%) of a pale yellow foam:  $[\alpha]_D^{22} -85^\circ$  (c 0.20,  $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3400, 2956, 1737, 1675, 1528, 1434, 1414, 1368, 1344, 1272, 1197, 1152, 1061;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.36-7.33 (3H, m), 7.04 (1H, d,  $J = 8.0$ ), 5.46 (1H, d,  $J = 7.8$ ), 5.19-5.16 (1H, m), 5.08 (2H, AB), 4.97 - 4.55 (1H, m), 4.69-4.55 (2H, m), 3.68 (3H, s), 3.30-3.10 (1H, m), 3.01-2.50 (4H, m), 2.40-2.33 (1H, m), 2.15-1.60 (5H, m), 1.44 (9H, s). Anal. Calcd for  $\text{C}_{28}\text{H}_{34}\text{Cl}_2\text{N}_4\text{O}_{10}$ : C, 51.15; H, 5.21; N, 8.52. Found: C, 51.35; H, 5.32; N, 8.56.

- [3S(1S,9S)] 5-(2,6-Dichlorobenzoyloxy)-3-[6,10-dioxo-9-(methoxycarbonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxopentanoic acid (284), was synthesized from 508a via method used to prepare 505 from 504 which afforded 330mg (65%) of a white solid: mp.  $115^\circ\text{C}$  (decomp.);  $[\alpha]_D^{20} -107^\circ$  (c 0.2,  $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3340, 2954, 1736, 1664, 1530, 1434, 1272, 1198, 1148, 1060;  $^1\text{H}$  NMR ( $\text{D}_6\text{-DMSO}$ )  $\delta$  8.91 (1H, d,  $J = 7.2\text{H}$ ), 7.67-7.63 (3H, m), 7.54 (1H, d,  $J = 8.0$ ), 5.24 (2H, s), 5.20-5.15 (1H, m), 4.79-4.70 (1H, m), 4.46-4.37 (2H, m), 3.58 (3H, s), 3.33-3.20 (1H, m), 2.94-2.55 (4H, m), 2.30-1.60 (6H,



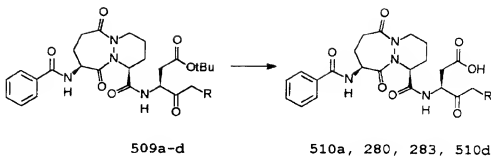
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m). Anal. Calcd for  $C_{24}H_{26}Cl_2N_4O_{10} \cdot H_2O$ : C, 46.54; H, 4.56; N, 9.05. Found: C, 46.36; H, 4.14; N, 8.88.

[3S(1S,9S)] t-Butyl 5-(2,6-dimethylbenzoyloxy)-3-[6,10-dioxo-9-(methoxycarbonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxopentanoate (508b), was synthesized by a similar method as compound 508a to afford a pale yellow foam (460mg, 82%):  $[\alpha]_D^{22} -115^\circ$  (c 0.20,  $CH_2Cl_2$ ); IR (KBr) 3413, 2960, 1729, 1675, 1528, 1514, 1461, 1421, 1368, 1265, 1116, 1096;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.27-7.03 (4H, m), 5.48 (1H, d, J = 8.2), 5.20-5.14 (1H, m), 5.04 (2H, AB), 4.93-4.86 (1H, m), 4.80-4.56 (2H, m), 3.77 (3H, s), 3.32-3.15 (1H, m), 3.00-2.56 (4H, m), 2.37 (6H, s), 2.19-1.77 (5H, m), 1.45 (9H, s), 2.41-2.25 (1H, m). MS ( $ES^+$ ) 617.

[3S(1S,9S)] 5-(2,6-Dimethylbenzoyloxy)3-[6,10-dioxo-9-(methoxycarbonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxopentanoic acid (285), was synthesized by a similar method as compound 284 to afford a white solid (303mg, 78%): mp.  $110^\circ C$  (decomp.);  $[\alpha]_D^{20} -128^\circ$  (c 0.10,  $CH_2Cl_2$ ); IR (KBr) 3339, 2958, 1731, 1666, 1529, 1420, 1266, 1248, 1115, 1070;  $^1H$  NMR ( $D_6$ -DMSO)  $\delta$  8.90 (1H, d, J = 7.4), 7.54 (1H, d, J = 7.9), 7.36-7.28 (1H, m), 7.17-7.14 (2H, m), 5.19-5.15 (3H, m), 4.84-4.74 (1H, m), 4.45-4.37 (2H, m), 3.59 (3H, s), 3.45-3.25 (1H, m), 2.95-2.64 (4H, m), 2.35 (6H, s), 2.30-1.60 (6H, m). Anal. Calcd for  $C_{26}H_{32}N_4O_{10} \cdot H_2O$ : C, 53.98; H, 5.92; N, 9.68. Found: C, 53.50; H, 5.52; N, 9.49. MS ( $ES^+$ ) 559.

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| compound                   | R |
|----------------------------|---|
| <b>509a</b><br><b>510a</b> |   |
| <b>509b</b><br><b>280</b>  |   |
| <b>509c</b><br><b>283</b>  |   |
| <b>509d</b><br><b>510d</b> |   |

[3*S*(1*S*,9*S*)] 3-(9-Benzoylamino-6,10-dioxo-

1,2,3,4,7,8,9,10-octahydro-6H-

pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-5-(2-

mercaptothiazole)-4-oxopentanoic acid (**510a**). A

15 solution of **506a** (2.27g, 4.2mmol) in dry

dichloromethane (50ml) was treated with 30% hydrobromic

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acid in acetic acid (1.84ml, 9.2mmol, 2.2equiv) at 0°C, under nitrogen. After 10min stirring at 0°C the reaction was complete and a white solid crystallised in the medium. The solid was filtered and washed with ethylacetate and diethylether to afford 2.20g (100%) of [3S(1S,9S)] 5-bromo-3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxopentanoic acid which was used without further purification: <sup>1</sup>H NMR (D<sub>6</sub>-DMSO) δ 8.87 (1H, d, J = 7.3), 8.63 (1H, d, J = 7.6), 7.91-7.87 (2H, m), 7.60-7.44 (3H, m), 6.92 (1H, bs), 5.14-5.09 (1H, m), 4.92-4.65 (2H, m), 4.43 (2H, AB), 4.41-4.35 (1H, m), 3.33-3.22 (1H, m), 2.98-2.90 (1H, m), 2.89-2.57 (2H, m), 2.35-2.15 (3H, m), 1.99-1.91 (2H, m), 1.75-1.60 (2H, m). A solution of the bromoketone (535mg, 1mmol) in dry DMF (10ml) was treated with potassium fluoride (150mg, 2.5mmol, 2.5 equiv), under nitrogen. After 5min stirring at room temperature, 2-mercaptothiazole (140mg, 1.2mmol, 1.2equiv) was added. After overnight reaction ethylacetate (150ml) was added and the organic solution was washed with brine, dried over magnesium sulphate and reduced in vacuo. The residue was crystallised in diethyl ether, filtered and purified on silica gel using a gradient of MeOH (0% to 5%) in dichloromethane. Evaporation afforded 344mg (60%) of a white solid: mp. 90-95°C (decomp.); [α]<sub>D</sub><sup>20</sup> -82° (c 0.2, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3328, 2941, 1745, 1659, 1535, 1422, 1276, 1255, 1223, 1072; <sup>1</sup>H NMR (D<sub>6</sub>-DMSO) δ 8.92 (1H, d, J = 7.6), 8.68 (1H, d, J = 7.6), 7.98-7.90 (2H, m), 7.75-7.67 (1H, m), 7.64-7.50 (4H, m), 5.22-5.18 (1H, m), 4.95-4.74 (2H, m), 4.58-4.38 (3H, m), 3.52-3.19 (1H, m), 3.05-2.65 (4H, m), 2.40-1.50 (6H, m). Anal.

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Calcd for  $C_{25}H_{27}N_5O_4S_2 \cdot H_2O$ : C, 50.75; H, 4.94 N, 11.84.  
Found: C, 51.34; H, 4.70; N, 11.58. MS ( $ES^+$ ) 572.

[3S(1S,9S)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-  
1,2,3,4,7,8,9,10-octahydro-6H-

- 5 pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5-  
(1-phenyl-1H-tetrazole-5-thio) pentanoate (509b). 507a  
(100mg, 0.17mmol) in dry dimethylformamide (1.5ml) was  
treated with 1-phenyl-1H-tetrazole-5-thiol (33mg,  
0.187mmol) and potassium fluoride (15mg, 0.34mmol).  
10 The mixture was stirred at room temperature for 2h,  
diluted with ethyl acetate, washed with aqueous sodium  
bicarbonate (x2), brine, dried ( $MgSO_4$ ) and evaporated.  
The product was purified by flash chromatography on  
silica gel eluting with ethyl acetate to give 103mg  
15 (88%) as a colourless foam:  $[\alpha]_D^{23}$  -92.2° (c 0.1,  
 $CH_2Cl_2$ ); IR (KBr) 3334, 1726, 1660, 1528, 1501, 1417,  
1394, 1368, 1279, 1253, 1155;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.82 (2H,  
m), 7.60-7.40 (8H, m), 7.39 (1H, d, J = 8.1), 7.05 (1H,  
d, J = 7.3), 5.26 (1H, m), 5.15 (1H, m), 4.99 (1H, m),  
20 4.60 (2H, m), 4.30 (1H, d, J = 17.2H), 3.32 (1H, m),  
3.10-2.75 (4H, m), 2.40 (1H, m), 2.24 (1H, m), 1.90  
(3H, m), 1.75 (1H, m), 1.44 (9H, s). MS ( $ES^+$ ) 691.47  
( $M^+ + 1$ ).

- [3S(1S,9S)] 3-(9-Benzoylamino-6,10-dioxo-  
25 1,2,3,4,7,8,9,10-octahydro-6H-  
pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-  
5-(1-phenyl-1H-tetrazole-5-thio) pentanoic acid (280),  
was synthesized via method used to prepare 505 from  
504. 509b (98mg, 0.142mmol) in dichloromethane (1ml)  
30 was cooled to 0° and trifluoroacetic acid (1ml) was  
added. The mixture was stirred at 0° for 15min and at

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room temperature for 30min before evaporation under reduced pressure. The residue was triturated with dry toluene and evaporated. Chromatography on silica gel eluting with 10% methanol in dichloromethane gave a

5 colourless glass which was crystallised from dichloromethane/diethyl ether to give 62mg (69%) of colourless solid: mp. 145°C (decomp.);  $[\alpha]_D^{22}$  -80.9° (c 0.1, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3400, 1727, 1658, 1530, 1501, 1460, 1445, 1416, 1280, 1254; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.00 (1H,

10 m), 7.79 (2H, d, J = 6.7), 7.58-7.30 (9H, m), 5.25 (2H, m), 4.94 (1H, m), 4.53 (2H, m), 4.35 (1H, m), 3.35 (1H, m), 3.01 (3H, m), 2.73 (1H, m), 2.38 (1H, m), 1.98 (4H, m), 1.64 (1H, m). Anal. Calcd for C<sub>29</sub>H<sub>30</sub>N<sub>8</sub>O<sub>7</sub>S•0.2TFA: C, 53.71; H, 4.63 N, 17.04. Found: C, 53.97; H, 4.92; N,

15 16.77. MS (ES<sup>+</sup>) 633.55 (M<sup>+</sup> - 1).

[3S(1S,9S)] t-Butyl 3-[9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-(3-pyridyloxy)pentanoate (509c), was prepared by a

20 similar method as compound 509b to afford a colourless glass (34%):  $[\alpha]_D^{22}$  -77.1° (c 0.25, CH<sub>2</sub>Cl<sub>2</sub>); IR (film) 3311, 1724, 1658, 1603, 1578, 1536, 1488, 1458, 1426, 1368, 1340, 1279, 1256, 1231, 1155, 707; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.29 (2H, m), 7.84 (2H, m), 7.48 (4H, m), 7.22 (3H,

25 m), 5.20 (2H, m), 4.90 (2H, m), 4.58 (1H, m), 3.29 (1H, m), 3.20-2.70 (4H, m), 2.38 (2H, m), 1.96 (4H, m), 1.68 (1H, m), 1.42 (9H, s). MS (ES<sup>+</sup>) 608.54 (M + 1).

[3S(1S,9S)] 3-[9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-

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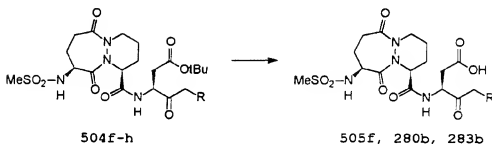
(3-pyridyloxy)pentanoic acid (**283**), was prepared by a similar method as compound **280** to afford a colourless foam (100%): mp. ~125°C;  $[\alpha]_D^{19}$  -84.1° (c 0.1, 20% MeOH/CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3401, 1736, 1663, 1538, 1469, 1459, 1425, 1281, 1258, 1200, 1134; <sup>1</sup>H NMR (CD<sub>3</sub>OD/CDCl<sub>3</sub>) δ 8.38 (2H, m), 7.84-7.40 (8H, m), 5.16 (4H, m), 4.80 (1H, m), 4.56 (1H, m), 3.50 (1H, m), 3.12 (2H, m), 2.82 (2H, m), 2.37 (1H, m), 2.10-1.65 (5H, m). Anal. Calcd for C<sub>27</sub>H<sub>29</sub>N<sub>5</sub>O<sub>8</sub>•0.4H<sub>2</sub>O: C, 51.77; H, 4.61; N, 10.41. Found: C, 52.19; H, 4.93; N, 9.99.

[**3S(1S,9S)**] t-Butyl 3-[6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-9-(phenylcarbonylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-(2-[4(3H)-pyrimidone])pentanoate (**509d**), was synthesized by a similar method as compound **509b** to afford a colourless solid (49.6mg, 82%): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.02 (1H, s), 7.95-7.86 (1H, m), 7.84-7.76 (2H, m), 7.62-7.35 (4H, m), 7.22-7.07 (1H, m), 6.43 (1H, d), 5.26-5.08 (2H, m), 5.03-4.72 (3H, m), 4.66-4.50 (1H, m), 3.43-3.19 (1H, m), 3.15-2.97 (1H, m), 2.86-2.72 (3H, m), 2.48-2.31 (1H, m), 2.18-1.60 (6H, m), 1.43 (9H, s).

[**3S(1S,9S)**] 3-[6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-9-(phenylcarbonylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-(2-[4(3H)-pyrimidone])pentanoic acid (**510d**), was synthesized by a similar method as compound **280** to afford a colourless solid (25.7mg, 57%): mp. 140-80°C; IR (KBr) 3391, 2945, 1733, 1664, 1530, 1422, 1363, 1277, 1259, 1204; <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 8.23 (1H, s), 7.94

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(1H, d), 7.87 (2H, d), 7.54-7.42 (3H, m), 6.48 (1H, d), 5.22-5.15 (1H, m), 4.57-4.46 (1H, m), 3.62-3.41 (1H, m), 3.22-3.13 (1H, m), 3.02-2.81 (2H, m), 2.70-1.80 (6H, m). Anal. Calcd for  $C_{26}H_{28}N_6O_8 \cdot 1.5H_2O$ : C, 54.30; H, 5.35; N, 14.61. Found: C, 54.14; H, 5.35; N, 13.04. MS ( $ES^+$ ) 551 (M - 1, 100%). Accurate mass calculated for  $C_{26}H_{29}N_6O_8$  ( $MH^+$ ): 553.2047. Found: 553.2080.



10

| compound     | R |
|--------------|---|
| 504f<br>505f |   |
| 504g<br>280b |   |
| 504h<br>283b |   |

15 [3*S*(1*S*,9*S*)] 5-(3-Chloro-2-oxy-4H-pyrido[1,2-a]pyrimidin-4-one)-3-[6,10-dioxo-9-

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- (methylsulphonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxopentanoic acid (505f), was prepared by a similar method as compound 508a using 507b and 3-chloro-2-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one and directly followed by the hydrolysis of 504f with trifluoroacetic to afford a tan powder (65mg, 30%):  $[\alpha]_D^{20}$  -128° (c 0.10, MeOH); IR (KBr) 3414, 2928, 1667, 1527, 2459, 1407, 1328, 1274, 1153, 1134;  $^1\text{H}$  NMR (MeOD)  $\delta$  9.35 (1H, d, J = 6.6H), 8.34 (1H, t, J = 7.2H), 7.99-7.95 (1H, m), 7.76-7.69 (1H, m), 5.85-5.45 (3H, m), 5.30-5.21 (1H, m), 4.93-4.66 (2H, m), 3.81-3.65 (1H, m), 3.66 (3H, m), 3.45-2.52 (4H, m), 2.52-1.71 (6H, m). D.J. Hlasta et al., J. Med. Chem. 1995, 38, 4687-4692.
- 15 [3S(1S,9S)] t-Butyl 3-(6,10-dioxo-9-methanesulphonamido-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5(1-phenyl-1H-tetrazole-5-thio)pentanoate (504g), was prepared by a similar method as compound 509b, (83%) as
- 20 a colourless foam:  $[\alpha]_D^{23}$  -112.7° (c 0.2,  $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3312, 1726, 1668, 1501, 1413, 1395, 1369, 1328, 1276, 1254, 1155;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.59 (5H, m), 7.48 (1H, d, J = 8.0), 5.68 (1H, d, J = 9.0), 5.37 (1H, m), 4.95 (1H, m), 4.62-4.31 (4H, m), 3.36 (1H, m), 2.98 (3H, s), 2.88 (4H, m), 2.66 (1H, m), 2.42 (2H, m), 1.98 (1H, m), 1.75 (1H, m), 1.43 (9H, s).
- 25 [3S(1S,9S)] 3-(6,10-Dioxo-9-methanesulphonamido-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5(1-phenyl-1H-tetrazole-5-thio)pentanoic acid (280b),
- 30



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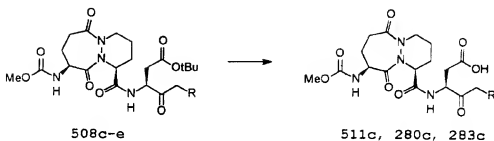
was prepared by a similar method as compound **280**,  
(100%) as a colourless foam: mp. 120-5°C;  $[\alpha]_D^{25}$  -  
112.4° (c 0.1, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3328, 1730, 1664,  
1529, 1501, 1410, 1328, 1277, 1219, 1153, 1134, 991; <sup>1</sup>H  
5 NMR (CDCl<sub>3</sub>) δ 8.07 (1H, d, J = 7.8), 7.58 (5H, s), 6.41  
(1H, d, J = 9.5), 5.32 (1H, m), 5.04 (1H, m), 4.70 (1H,  
d, J = 17.5), 4.60 (3H, m), 3.50-2.9 (3H, m), 2.98 (3H,  
s), 2.45 (2H, m), 2.06 (4H, m), 1.68 (1H, m).

[3S(1S,9S)] t-Butyl 3-(6,10-dioxo-9-  
10 methanesulphonamido-1,2,3,4,7,8,9,10-octahydro-6H-  
pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-  
5(3-pyridyloxy)pentanoate (**504h**), was prepared by a  
similar method as compound **509b** (24%) as a colourless  
foam:  $[\alpha]_D^{23}$  -101.0° (c 0.2, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3330,  
15 1727, 1669, 1425, 1396, 1369, 1328, 1276, 1256, 1231,  
1155, 1137, 991; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.28 (2H, br d, J =  
9.4), 7.71 (1H, d, J = 7.9), 7.22 (2H, s), 6.03 (1H, d,  
J = 9.4), 5.36 (1H, m), 4.95 (2H, m), 4.52 (2H, m),  
3.29 (1H, m), 3.07 (3H, s), 3.23-2.75 (3H, m), 2.66-  
20 2.35 (2H, m), 2.30-1.60 (5H, m), 1.42 (9H, s).

[3S(1S,9S)] 3-(6,10-Dioxo-9-methanesulphonamido-  
1,2,3,4,7,8,9,10-octahydro-6H-  
pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-  
5(3-pyridyloxy)pentanoic acid (**283b**), was prepared by a  
25 similar method as compound **280**, (100%) as a colourless  
foam: mp. 120-5°C;  $[\alpha]_D^{25}$  -85.2° (c 0.1, 10%  
CH<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3337, 1738, 1667, 1560, 1457,  
1424, 1326, 1317, 1278, 1258, 1200, 1189, 1150, 1133,  
991; <sup>1</sup>H NMR (CDCl<sub>3</sub>/CD<sub>3</sub>OD) δ 8.35 (2H, m), 7.54 (2H, m),

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5.32 (2H, m), 4.83 (2H, m), 4.45 (2H, m), 3.43-2.77 (4H, m), 2.97 (3H, s), 2.42 (2H, m), 2.05-1.72 (5H, m).



5

| compound     | R |
|--------------|---|
| 508c<br>511c |   |
| 508d<br>280c |   |
| 508e<br>283c |   |

10

[3*S*(1*S*,9*S*)] t-Butyl 3-[6,10-dioxo-9-(methoxycarbonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-5-(2-mercaptopyrimidine)-4-oxo-pentanoate (508c), was prepared by a similar method as compound 509b to afford 544mg (97%) of a pale yellow foam:  $[\alpha]_D^{20}$  -86° (c 0.19, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3426, 2947, 1725, 1669, 1551, 1418,

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1383, 1253, 1155, 1064;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.49 (2H, d,  $J$  = 4.8), 7.13 (1H, d,  $J$  = 7.9), 7.03-6.98 (1H, m), 5.47 (1H, d,  $J$  = 7.9), 5.23-5.19 (1H, m), 5.09-5.01 (1H, m), 4.84-4.51 (2H, m), 4.04 (2H, AB), 3.69 (3H, s), 3.38-3.19 (1H, m), 3.06-2.64 (4H, m), 2.40-1.76 (6H, m), 1.43 (9H, s). Anal. Calcd for  $\text{C}_{25}\text{H}_{34}\text{N}_6\text{O}_8\text{S}$ : C, 51.89; H, 5.92; N, 14.52. Found: C, 51.49; H, 6.04; N, 13.87. MS ( $\text{ES}^+$ ) 579.

[3S(1S,9S)] 3-[6,10-Dioxo-9-(methoxycarbonyl)-amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-5-(2-mercaptopyrimidine)-4-oxopentanoic acid (511c), was prepared by a similar method as compound 280 to afford 370mg (79%) of a white powder: mp. 105°C (dec);  $[\alpha]_{\text{D}}^{22}$  -94° (c 0.20,  $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3316, 3057, 2957, 1724, 1664, 1252, 1416, 1384, 1254, 1189, 1063;  $^1\text{H}$  NMR ( $\text{D}_6$ -DMSO)  $\delta$  8.85 (1H, d,  $J$  = 7.8), 8.62 (2H, d,  $J$  = 4.7), 7.53 (1H, d,  $J$  = 8.0), 7.28-7.23 (1H, m), 5.21-5.17 (1H, m), 4.87-4.79 (1H, m), 4.47-4.35 (2H, m), 4.23 (2H, AB), 3.58 (3H, s), 3.30-3.21 (1H, m), 2.95-2.50 (4H, m), 2.35-1.60 (6H, m). Anal. Calcd for  $\text{C}_{21}\text{H}_{26}\text{N}_6\text{O}_8\text{S} \cdot \text{H}_2\text{O}$ : C, 46.66; H, 5.22; N, 15.55. Found: C, 46.66; H, 5.13; N, 15.07. MS ( $\text{ES}^+$ ) 523, ( $\text{ES}^+$ ) 521.

[3S(1S,9S)] t-Butyl 3-[6,10-dioxo-9-(methoxycarbonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-[5-(1-phenyltetrazolyl)-thio]pentanoate (508d), was synthesized by a similar method as compound 509b to afford a colourless solid (269mg, 87%): mp. 80-110°C;  $[\alpha]_{\text{D}}^{23}$  -108° (c 0.60  $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3315, 2977, 1727,

- 622 -

1688, 1527, 1501, 1458, 1418, 1368, 1279, 1250, 1155, 1064;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.70 (1H, d), 7.63-7.53 (5H, m), 5.84 (1H, d), 5.34-5.27 (1H, m), 5.05-4.92 (1H, m), 4.78-4.54 (3H, m), 4.38 (1H, d), 3.66 (3H, s), 3.37-3.19 (1H, m), 3.07-2.94 (1H, m), 2.91-2.82 (2H, m), 2.71-2.56 (1H, m), 2.40-2.30 (1H, m), 2.19-2.13 (1H, m), 2.08-1.68 (4H, m), 1.42 (9H, s). MS ( $\text{ES}^+$ ) 667 (31%), 645 ( $\text{M}^+ + 1$ , 100), 589 (62).

[3S(1S,9S)] 3-[6,10-Dioxo-9-(methoxycarbonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-[5-(1-phenyltetrazolyl)-thio]pentanoic acid (280c), was synthesized by a similar method as compound 280 to afford a pale cream solid (203mg, 88%): mp. 105-130°C;  $[\alpha]_{\text{D}}^{22}$  -235° (c 0.11 MeOH); IR (KBr) 3342, 2951, 1727, 1667, 1529, 1501, 1459, 1416, 1276, 1252, 1225, 1192, 1062;  $^1\text{H}$  NMR ( $\text{D}_6$ -DMSO)  $\delta$  8.89 (1H, d), 7.69 (5H, s), 7.50 (1H, d), 5.18-5.11 (1H, m), 4.79-4.69 (1H, m), 4.57 (2H, s), 4.42-4.32 (1H, m), 3.54 (3H, s), 2.92-2.63 (3H, m), 2.21-1.82 (5H, m), 1.65-1.57 (1H, m). MS ( $\text{ES}^+$ ) 587 ( $\text{M} - 1$ , 100%).

[3S(1S,9S)] t-Butyl 3-[6,10-dioxo-9-(methoxycarbonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-(3-pyridinyloxy) pentanoate (508e), was synthesized by a similar method as compound 509b to afford a pale orange solid (199mg, 25%): mp. 80-120°C;  $[\alpha]_{\text{D}}^{23}$  -89° (c 0.51  $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3333, 2978, 1726, 1669, 1576, 1536, 1478, 1426, 1368, 1277, 1253, 1232, 1155, 1064;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.41-8.18 (2H, m), 7.81 (1H, d), 7.26-



- 623 -

7.20 (2H, s), 5.91 (1H, d), 5.24-5.16 (1H, m), 5.07-4.86 (3H, m), 4.81-4.51 (2H, m), 3.67 (3H, s), 3.34-3.16 (1H, m), 3.10-2.81 (3H, m), 2.72-2.54 (1H, m), 2.41-2.31 (1H, m), 2.07-1.62 (5H, m), 1.47 (9H s). MS (ES<sup>+</sup>) 562 (M<sup>+</sup> + 1, 100%), 506 (38).

[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-9-(methoxycarbonylamino)-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido]-4-oxo-5-(3-pyridinyloxy)pentanoic acid (283c), was synthesized by a similar method as compound 280 to afford an off-white powder (167mg, 98%): mp. 90-105°C; [ $\alpha$ ]<sub>D</sub><sup>22</sup> -106° (c 0.11 MeOH); IR (KBr) 3325, 3070, 2956, 1669, 1544, 1423, 1256, 1199, 1133, 1062; <sup>1</sup>H NMR (D<sub>6</sub>-DMSO)  $\delta$  8.95 (1H, d), 8.45-8.20 (2H, m), 7.53-7.45 (3H, m), 5.19-5.08 (3H, m), 4.70-4.62 (1H, m), 4.41-4.30 (2H, m), 3.53 (3H, s), 2.92-2.68 (3H, m), 2.22-2.06 (2H, m), 1.95-1.82 (2H, m), 1.63-1.53 (1H, m). MS (ES<sup>+</sup>) 506 (M<sup>+</sup> + 1, 100%).



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| compound     | R   |
|--------------|---|
| 512a<br>280d |  |
| 512b<br>283d |  |

5

[3*S*(1*S*,9*S*)] *t*-Butyl 3-(9-acetamido-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-4-oxo-5-(1-phenyl-1H-tetrazole-5-thio)pentanoate (512a), was

10 prepared by a similar method as compound 509b, to afford (83%) as a colourless foam:  $[\alpha]_D^{23}$  -129.6° (c 0.1, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3323, 1726, 1664, 1531, 1501, 1444, 1415, 1394, 1369, 1279, 1254, 1156; <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.7.59 (5H, s), 7.37 (1H, d, *J* = 7.9), 6.38 (1H, d, *J* = 7.4), 5.27 (1H, m), 4.98 (2H, m), 4.58 (2H, d + m), 4.28 (1H, d, *J* = 17.2), 3.28 (1H, m), 3.10-2.65 (4H, m), 2.31 (2H, m), 2.03 (3H, s), 2.10-1.72 (4H, m), 1.48 (9H, s).

[3*S*(1*S*,9*S*)] 3-(9-Acetamido-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-4-oxo-5-(1-phenyl-1H-tetrazole-5-thio)pentanoic acid (280d), was prepared by a similar method as compound 280, to afford (77%) as a colourless foam:  $[\alpha]_D^{22}$  -93.3° (c 0.1, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3316,

20

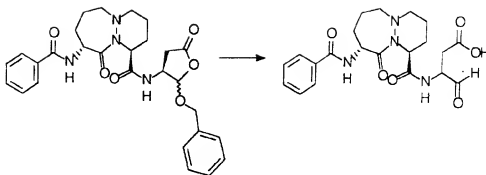
- 625 -

1728, 1659, 1531, 1501, 1415, 1341, 1278, 1253, 1222, 1185;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.05 (1H, d,  $J = 7.9$ ), 7.57 (5H, br s), 5.30 (1H, m), 5.01 (2H, m), 4.70-4.10 (4H, m), 3.40-2.85 (4H, m), 2.62 (1H, m), 2.33 (1H, m), 2.27-  
5 1.65 (5H, m), 2.01 (3H, s).

[3S(1S,9S)] t-Butyl 3-(9-acetamido-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5-(3-pyridyloxy)pentanoate (512b), was prepared by a  
10 similar method as compound 509b, to afford (9%) as a colourless foam: IR (KBr) 3333, 1727, 1661, 1542, 1427, 1369, 1279, 1257, 1232, 1156;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.30 (2H, m), 7.20 (3H, m), 6.45 (1H, d,  $J = 7.4$ ), 5.17 (1H, m), 4.91 (3H, m), 4.55 (1H, m), 3.27 (1H, m), 3.14-2.70  
15 (4H, m), 2.41 (1H, m), 2.04 (3H, s), 2.10-1.65 (6H, m), 1.44 (9H, s).

[3S(1S,9S)] 3-(9-Acetamido-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5-(3-pyridyloxy)pentanoic acid  
20 (283d), was prepared by a similar method as compound 280. (100%) as a colourless foam:  $[\alpha]_{\text{D}}^{22} -106.0^\circ$  (c 0.2, 10%  $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3312, 1735, 1664, 1549, 1426, 1279, 1258, 1200, 1135;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.27 (2H, m), 7.46 (2H, m), 5.09 (1H, m), 4.79 (3H, m), 4.47 (1H, m),  
25 3.40 (1H, m), 3.30-2.70 (3H, m), 2.54 (1H, m), 2.30 (1H, m), 1.98 (3H, s), 2.05-1.65 (4H, m).

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245b

246b

- [1*S*,9*R*(2*RS*,3*S*)] 9-Benzoylamino-*N*-(2-benzoyloxy-5-oxotetrahydrofuran-3-yl)-1,2,3,4,7,8,9,10-octahydro-10-oxo-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide (245b), was prepared from [1*S*,9*R*] 9-Benzoylamino-1,2,3,4,7,8,9,10-octahydro-10-oxo-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxylic acid by the method described for 245 to afford 416mg (85%) of a colourless foam (~1:1 mixture of diastereoisomers): IR (KBr) 3392, 3302, 2942, 1792, 1642, 1529, 1520, 1454, 1119; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.79 (2H, m), 7.51-7.09 (10H, m), 5.52 (0.5H, d, *J* = 5.3), 5.51 (0.5H, s), 5.36 (1H, m), 4.84 (1H, m), 4.74-4.59 (1.5H, m), 4.51 (1H, m), 4.38 (0.5H, m), 3.22-2.83 (5H, m), 2.51 (1H, m), 2.25 (2H, m), 2.01-1.46 (6H, m). Anal. Calcd for C<sub>28</sub>H<sub>32</sub>N<sub>4</sub>O<sub>6</sub>•0.75H<sub>2</sub>O: C, 62.97; H, 6.32; N, 10.49. Found: C, 63.10; H, 6.16; N, 10.21. MS (ES<sup>+</sup>) 521 (*M* + 1, 100%).

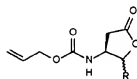
- [3*S*(1*S*,9*R*)] 3-(9-Benzoylamino-1,2,3,4,7,8,9,10-octahydro-10-oxo-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (246b), was prepared from 245b by the method described for 246 to afford



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104mg (33%) of a white powder: mp. 115-119°C;  $[\alpha]_D^{24}$  - 19.8° (c 0.2 MeOH); IR (KBr) 3293, 2944, 1786, 1639, 1576, 1537, 1489, 1450, 1329, 1162, 1124;  $^1\text{H}$  NMR (CD<sub>3</sub>OD)  $\delta$  7.85 (2H, d,  $J$  = 7.0), 7.49 (3H, m), 5.49 (1H, m), 4.55 (1H, m), 4.30 (2H, m), 3.40 (1H, m), 3.19-2.89 (3H, m), 2.63 (2H, m), 2.16-1.81 (5H, m), 1.60 (3H, m). Anal. Calcd for C<sub>21</sub>H<sub>26</sub>N<sub>4</sub>O<sub>6</sub>·H<sub>2</sub>O: C, 56.24; H, 6.29; N, 12.49. Found: C, 56.54; H, 6.05; N, 12.29. MS (ES<sup>+</sup>) 429 (M - 1, 100%).








10 Compounds **513a-j** were prepared as described below.

**513a-f**

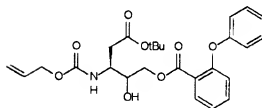
| compound      | R |
|---------------|---|
| <b>513a</b>   |   |
| <b>513a-1</b> |   |
| <b>513a-2</b> |   |
| <b>513b</b>   |   |
| <b>513b-1</b> |   |

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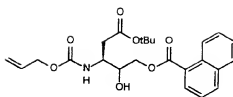
|        |   |
|--------|---|
| 513b-2 |  |
| 513c   |  |
| 513d   |  |
| 513e   |  |
| 513f   |  |
| 513f-1 |  |
| 513f-2 |  |

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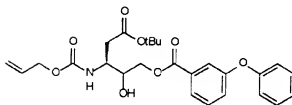


513g

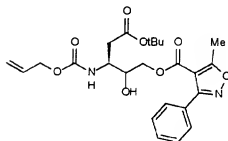
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513h



513i



513j

(2*RS*,3*S*) 3-(Allyloxycarbonyl)amino-2-(2-phenethyloxy)-  
 5 5-oxotetrahydrofuran (513a), was prepared by a similar  
 method as compound 513d/e to afford a mixture of  
 diastereoisomers (670mg, 50%) as an oil: IR (KBr) 3331,  
 2946, 1790, 1723, 1713, 1531, 1329, 1257, 1164, 1120,  
 1060, 977, 937, 701; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.36-7.18 (5H, m),  
 10 5.99-5.83 (1H, m), 5.41-5.34 (2H, m), 5.28-5.18 (2H,

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m), 4.59-4.56 (2H, m), 4.32-3.96 (2H, m), 3.85-3.73 (1H, m), 3.02-2.76 (3H, m), 2.49-2.34 (1H, m).

(2*RS*,3*S*) 3-(Allyloxycarbonyl)amino-2-cyclopentyloxy-5-oxotetrahydrofuran (513b), was prepared as 513d/e to

- 5 afford 8g (51%) of a mixture of diastereoisomers as a clear oil:  $[\alpha]_D^{20}$  -13° (c 0.25, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3325, 2959, 2875, 1790, 1723, 1535, 1420, 1328, 1257, 1120, 1049, 973, 937; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 6.02-5.80 (1H, m), 5.53-5.46 (2H, m), 5.37-5.21 (2H, m), 4.58 (2H, d, J = 5.5),  
10 4.50-4.46 (0.5H, m), 4.34-4.25 (1H, m), 4.19-4.12 (0.5H, m), 3.06-2.77 (1H, m), 2.53-2.35 (1H, m), 1.85-1.50 (8H, m). Anal. Calcd for C<sub>13</sub>H<sub>19</sub>NO<sub>5</sub>: C, 57.98; H, 7.11; N, 5.20. Found: C, 56.62; H, 7.22; N, 4.95. MS (ES<sup>+</sup>) 270.

- 15 (2*R*,3*S*) 3-Allyloxycarbonylamino-2-(indan-2-yloxy)-5-oxotetrahydrofuran (513c), was synthesized by a similar method as compound 513d/e to afford a single isomer (20%) as a pale yellow oil:  $[\alpha]_D^{24}$  -63.1° (c 0.2, CH<sub>2</sub>Cl<sub>2</sub>); IR (film) 3338, 2948, 1791, 1723, 1529, 1421,  
20 1330, 1253, 1122, 984, 929, 746; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.20 (4H, m), 5.87 (1H, m), 5.61 (1H, d, J = 5.4), 5.33-5.10 (2H, m), 4.70 (1H, m), 4.56 (3H, m), 3.33-3.19 (2H, m), 3.10-2.94 (2H, m), 2.81 (1H, dd, J = 8.3, 17.3), 2.43 (1H, dd, J = 10.5, 17.3).

- 25 (2*R*,3*S*) 3-Allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydro-furan (513d) and (2*S*,3*S*) 3-Allyloxycarbonylamino-2-benzyloxy-5-oxo-tetrahydrofuran (513d/e), were prepared [via method described by Chapman Biorg. & Med. Chem. Lett., 2, pp. 615-618

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(1992)]. Following work-up by extraction with ethylacetate and washing with  $\text{NaHCO}_3$ , the product was dried ( $\text{MgSO}_4$ ), filtered and evaporated to yield an oil which contained product and benzyl alcohol. Hexane (200ml) (200ml hexane for every 56g of AllocAsp( $\text{CO}_2\text{tBu}$ ) $\text{CH}_2\text{OH}$  used) was added and the mixture stirred and cooled overnight. This afforded an oily solid. The liquors were decanted and retained for chromatography. The oily residue was dissolved in ethyl acetate and evaporated to afford an oil which was crystallised from 10% ethyl acetate in hexane (~500ml). The solid was filtered to afford **513d** (12.2g, 19%): mp. 108-110°C;  $[\alpha]_D^{24} +75.72^\circ$  (c 0.25,  $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3361, 1778, 1720, 1517, 1262, 1236, 1222, 1135, 1121, 944, 930, 760;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.38 (5H, m), 5.90 (1H, m), 5.50 (1H, s), 5.37 (0.5H, m), 5.26 (2.5H, m), 4.87 (1H, ABq), 4.63 (3H, m), 4.31 (1H, m), 3.07 (1H, dd), 2.46 (1H, dd). Anal. Calcd for  $\text{C}_{15}\text{H}_{17}\text{NO}_5$ : C, 61.85; H, 5.88; N, 4.81. Found: C, 61.85; H, 5.89; N, 4.80.

The liquors were combined and evaporated to yield an oil (~200g) containing benzyl alcohol. Hexane/ethyl acetate (9:1, 100ml) was added and the product purified by chromatography eluting with 10% ethyl acetate in hexane to remove the excess benzyl alcohol, and then dichloromethane/hexane (1:1 containing 10% ethyl acetate). This afforded **513e** containing some **513d** (20.5g, 32%): mp. 45-48°C;  $[\alpha]_D^{24} -71.26^\circ$  (c 0.25,  $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3332, 1804, 1691, 1536, 1279, 1252, 1125, 976.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.38 (5H, m), 5.91 (1H, m), 5.54 (1H, d, J = 5.2), 5.38 (3H, m), 4.90 (1H, ABq), 4.60 (4H, m), 2.86 (1H, dd), 2.52 (1H,

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dd). Anal. Calcd for  $C_{15}H_{17}NO_5 \cdot 0.1H_2O$ : C, 61.47; H, 5.91; N, 4.78. Found: C, 61.42; H, 5.88; N, 4.81.

**(2*RS*,3*R*) 3-(Allyloxycarbonylamino)-2-ethoxy-5-oxotetrahydrofuran (513f)**, was synthesized by a similar

5 method as 513d/e to afford a colourless oil (152mg, 79%): IR (film) 3334, 2983, 2941, 1783, 1727, 1713, 1547, 1529, 1422, 1378, 1331, 1313, 1164, 1122, 1060, 938;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  6.09-5.82 (2H, m), 5.50-5.18 (3H, m), 4.64-4.54 (2H, m), 4.27-4.16 (1H, m), 3.95-3.78 (1H, m), 3.73-3.56 (1H, m), 3.05-2.77 (1H, m), 2.56-2.37 (1H, m), 1.35-1.17 (4H, m). Anal. Calcd for  $C_{10}H_{15}NO_5$ : C, 52.40; H, 6.60; N, 6.11. Found: C, 52.16; H, 6.62; N, 5.99. MS ( $ES^+$ ) 229 ( $M^+ + 1$ , 100%).

**(3*S*,4*RS*) t-Butyl 3-(allyloxycarbonylamino)-4-hydroxy-5-(2-phenoxybenzoyloxy)pentanoate (513g)**. 4-

15 Dimethylamino-pyridine (76.0mg, 622mmol) was added to a solution of 2-phenoxybenzoyl chloride (579mg, 2.49mmol) and 517 (600mg, 2.07mmol) in pyridine (10ml). The mixture was stirred at room temperature for 18h before  
20 adding brine (25ml) and extracting with ethyl acetate (30ml, 20ml). The combined organic extracts were washed with 1M hydrochloric acid (3 x 25ml), saturated aqueous sodium hydrogen carbonate (2 x 25ml) and brine (25ml), dried ( $MgSO_4$ ) and concentrated. The pale  
25 orange oil was purified by flash column chromatography (1-10% acetone in dichloromethane) to afford 447mg (44%) of colourless oil: IR (film) 3375, 2980, 1721, 1712, 1602, 1579, 1514, 1484, 1451, 1368, 1294, 1250, 1234, 1161, 1137, 1081, 754;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.98-7.93 (1H, m), 7.50-7.41 (1H, m), 7.35-7.25 (2H, m), 7.22-7.03 (3H, m), 6.95 (3H, d), 5.95-5.76 (1H, m), 5.57

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(1H, d), 5.30-5.13 (2H, m), 4.51 (2H, d), 4.25 (2H, d), 4.18-4.04 (1H, m), 3.88 (1H, m), 3.50 (1H, m), 2.51 (2H, m), 1.41 (9H, s). MS (ES<sup>+</sup>) 508 (57%), 503 (76%), 486 (M<sup>+</sup> + 1, 45), 468 (27), 412 (100). Accurate mass  
5 calculated for C<sub>26</sub>H<sub>32</sub>NO<sub>8</sub> (MH<sup>+</sup>): 486.2128. Found: 486.2158.

(3S,4R) t-Butyl (N-allyloxycarbonyl)-3-amino-4-hydroxy-5-(1-naphthoyloxy)pentanoate (513h), was prepared from  
(3S,4R) t-butyl (N-allyloxycarbonyl)-3-amino-4,5-  
10 dihydroxypentanoate by the method described for 513g to afford 562mg (85%) of a colourless oil: IR (film) 3418, 2980, 1722, 1711, 1512, 1368, 1278, 1245, 1198, 1157, 1139; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.90 (1H, d, J = 8.6), 8.21 (1H, dd, J = 1.2, 7.3), 8.04 (1H, d, J = 8.2), 7.89 (1H, dd,  
15 J = 1.5, 7.9), 7.67-7.46 (3H, m), 5.88 (1H, m), 5.49 (1H, d, J = 9.0), 5.35-5.18 (2H, m), 4.57-4.46 (4H, m), 4.19 (2H, m), 2.67 (2H, m), 1.40 (9H, s). Anal. Calcd for C<sub>24</sub>H<sub>29</sub>NO<sub>7</sub>: C, 65.00; H, 6.59; N, 3.16. Found: C, 64.74; H, 6.56; N, 3.09. M.S. (ES<sup>+</sup>) 466 (M+Na, 100%),  
20 444 (M+1, 39), 388 (44).

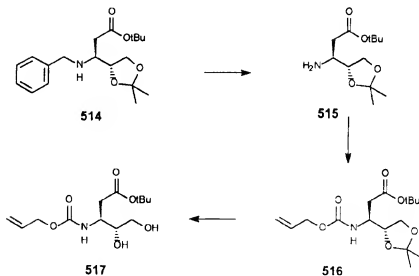
(3S,4RS) t-Butyl 3-(allyloxycarbonylamino)-4-hydroxy-5-(3-henoxybenzoyloxy)pentanoate (513i), was synthesized by a similar method as compound 513g to afford a colourless oil (569mg, 85%): IR (film) 3400, 1723,  
25 1712, 1584, 1528, 1489, 1443, 1367, 1276, 1232, 1190, 1161, 1098, 1074, 995, 755; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.65-8.59 (1H, d), 7.84-7.66 (2H, m), 7.45-7.11 (5H, m), 7.05-6.97 (2H, m), 6.00-5.78 (1H, m), 5.54-5.14 (2H, m), 4.62-4.52 (2H, m), 4.42-4.32 (2H, m), 4.08-4.22 (2H, m),  
30 2.78-2.47 (2H, m), 1.44 (9H, s). MS (ES<sup>+</sup>) 508 (100%),

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486 ( $M^+ + 1$ , 33. Accurate mass calculated for  $C_{26}H_{32}NO_8$  ( $MH^+$ ): 486.2128. Found: 486.2121.

(3*S*,4*RS*) t-Butyl 3-(allyloxycarbonylamino)-4-hydroxy-5-(5-methyl-3-phenylisoxazoloyloxy)pentanoate (513j), was  
 5 synthesized by a similar method as compound 513g to afford a pale orange oil (905mg, 91%): IR (film): 3418, 3383, 2980, 1722, 1711, 1601, 1517, 1450, 1424, 1368, 1308, 1252, 1154, 1100, 994, 767, 698;  $^1H$  NMR ( $CDCl_3$ )  $\delta$   
 7.62-7.55 (2H, m), 7.51-7.42 (3H, m), 5.98-5.76 (1H, 10 m), 5.33-5.18 (2H, m), 4.53 (2H, d), 4.18 (2H, d), 3.91 (1H, m), 3.80 (1H, m), 2.76 (3H, s), 2.50 (2H, m), 1.43 (9H, s). Anal. Calcd for  $C_{24}H_{30}N_2O_8 \cdot 0.5H_2O$ : C, 59.62; H, 6.46; N, 5.79. Found: C, 59.46; H, 6.24; N, 5.72. MS ( $ES^+$ ) 497 (100%), 475 ( $M^+ + 1$ , 15), 419 (48).

15



(3*S*,4*RS*) t-Butyl 3-benzylamino-4,5-(dimethylmethylenedioxy)-pentanoate (514), was prepared by the method described in H. Matsunaga, et al.



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Tetrahedron Letters 24, pp. 3009-3012 (1983) as a pure diastereomer (60%) as an oil:  $[\alpha]_D^{23} -36.9^\circ$  (c 0.5, dichloromethane); IR (film) 2982, 2934, 1726, 1455, 1369, 1257, 1214, 1157, 1068;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.31 (5H, m), 4.10 (1H, q,  $J = 6.0$ ), 4.05-3.75 (4H, m), 3.10 (1H, q,  $J = 6.0$ ), 2.40 (2H, m), 1.42 (9H, s), 1.40 (3H, s), 1.34 (3H, s).

**(3S,4R) t-Butyl 3-(allyloxycarbonylamino)-4,5-(dimethylmethylenedioxy)pentanoate (516).** 514 (3.02g, 9.00mmol) and 10% palladium on carbon (300mg) in ethanol (30ml) were stirred under hydrogen for 2h. The suspension was filtered through celite and a 0.45mm membrane and the filtrate concentrated to give a colourless oil **515** (2.106g, 95%) which was used without purification. The oil (1.93g, 7.88mmol) was dissolved in water (10ml) and 1,4-dioxan and sodium hydrogen carbonate added (695mg, 8.27mmol). The mixture was cooled to  $0^\circ\text{C}$  and allyl chloroformate (1.04g, 9.19ml, 8.66mmol) added dropwise. After 3h the mixture was extracted with ether (2 x 50ml). The combined ether extracts were washed with water (2 x 25ml) and brine (25ml), dried ( $\text{MgSO}_4$ ) and concentrated to give a colourless oil. Flash column chromatography (10-35% ethylacetate in hexane) afforded a colourless solid (2.69g, 95%): mp.  $64-5^\circ\text{C}$ ;  $[\alpha]_D^{23} -21^\circ$  (c 1.00,  $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3329, 1735, 1702;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  6.00-5.82 (1H, m), 5.36-5.14 (2H, m), 5.42 (1H, s), 4.56 (1H, d), 4.40-4.06 (2H, m), 4.03 (1H, m), 3.70 (1H, m), 2.52 (2H, m), 1.44 (12H, 2 x s), 1.33 (3H, s); Anal. Calcd for  $\text{C}_{16}\text{H}_{27}\text{NO}_6$ : C, 58.34; H, 8.26; N, 4.25. Found: C, 58.12; H, 8.16; N, 4.19; MS (+FAB) 320 ( $\text{M}^+ + 1$ , 41%), 274 (70), 216 (100).

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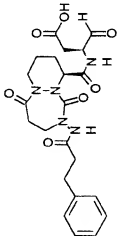
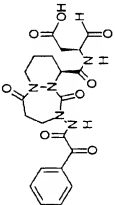
(3*S*,4*R*) *t*-Butyl 3-(allyloxycarbonylamino)4,5-dihydroxy pentanoate (517). A solution 516 (2.44g, 7.41mmol) in 80% aqueous acetic acid (25ml) was stirred at room temperature for 24h then concentrated and azeotroped with toluene (2 x 25ml). The residue was treated with brine (25ml) and extracted with ethylacetate (2 x 25ml). The organic fractions were dried (MgSO<sub>4</sub>) and concentrated to afford a colourless oil. Flash chromatography (20-80% ethyl acetate in dichloromethane) gave a colourless solid (1.99g, 90%): mp. 74-5°C;  $[\alpha]_D^{25}$  -1.3° (c 1.0, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 1723, 1691; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 6.02-5.78 (2H, m), 5.35-5.16 (2H, m), 4.55 (2H, d), 4.16-4.04 (2H, m), 2.76 (2H, s), 3.56 (2H, m), 2.56 (2H, m), 1.43 (9H, s); Anal. Calcd for C<sub>13</sub>H<sub>23</sub>NO<sub>6</sub>: C, 53.97; H, 8.01; N, 4.84. Found: C, 53.79; H, 7.88; N, 4.81; MS(+FAB) 290 (M<sup>+</sup>+1, 44%), 234 (100).

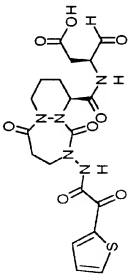
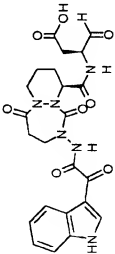
#### Example 30

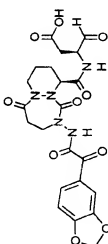
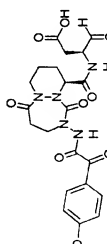
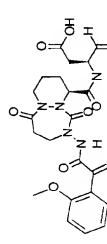
Compounds 1105-1125 were prepared as follows.

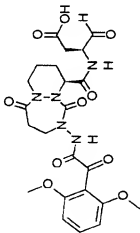
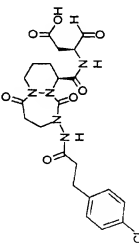
Physical data for these compounds is listed in Table 24.

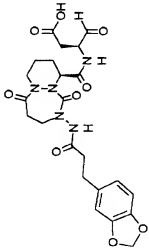
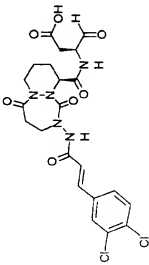
Table 24

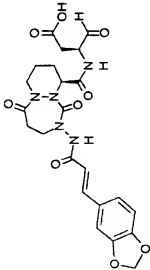
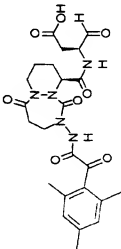
| Compound | Structure  | MF         | MW     | HPLC RT min<br>(method)<br>Purity | MS<br>(M+Na) + |
|----------|--|------------|--------|-----------------------------------|----------------|
| 1105     |  | C22H27N5O7 | 473.49 | 12.769 (1)<br>99%                 | 496.9          |
| 1106     |  | C21H23N5O8 | 473.45 | 12.137 (1)<br>99%                 | 496.9          |

| Compound | Structure  | MF  | MW     | HPLC RT min<br>(method)<br>Purity | MS<br>(M+Na)+ |
|----------|--|---|--------|-----------------------------------|---------------|
| 1107     |  | C <sub>19</sub> H <sub>21</sub> N <sub>5</sub> O <sub>8</sub> S | 479.47 | 11.272 (1)<br>97%                 | 502.9         |
| 1108     |  | C <sub>23</sub> H <sub>24</sub> N <sub>6</sub> O <sub>8</sub>   | 512.48 | 13.699 (1)<br>97%                 | 536.4         |

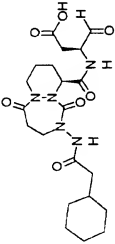
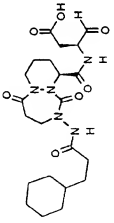
| Compound | Structure  | MF          | MW     | HPLC RT min<br>(method)<br>Purity | MS<br>(M+Na)+ |
|----------|--|-------------|--------|-----------------------------------|---------------|
| 1109     |  | C22H23N5O10 | 517.46 | 12.341 (1)<br>92%                 | 541.2         |
| 1110     |  | C22H25N5O9  | 503.47 | 12.991 (1)<br>96%                 | 527.9         |
| 1111     |  | C22H25N5O9  | 503.47 | 10.951 (1)<br>99%                 | 526.7         |

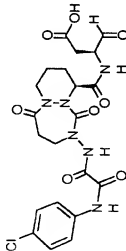
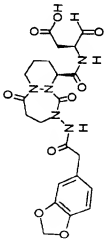
| Compound | Structure  | MF           | MW     | HPLC RT min<br>(method)<br>Purity | MS<br>(M+Na)+ |
|----------|--|--------------|--------|-----------------------------------|---------------|
| 1112     |  | C23H27N5O10  | 533.50 | 11.377 (1)<br>98%                 | 557.2         |
| 1113     |  | C22H26ClN5O7 | 507.93 | 16.317 (1)<br>98%                 | 531.5         |

| Compound | Structure  | MF  | MW     | HPLC RT min<br>(method)<br>Purity | MS<br>(M+Na) <sup>+</sup> |
|----------|--|---|--------|-----------------------------------|---------------------------|
| 1114     |  | C <sub>23</sub> H <sub>27</sub> N <sub>5</sub> O <sub>9</sub>                 | 517.50 | 12.902 (1)<br>99%                 | 542.4                     |
| 1115     |  | C <sub>22</sub> H <sub>23</sub> Cl <sub>2</sub> N <sub>5</sub> O <sub>7</sub> | 540.36 | 12.529 (2)<br>97%                 | 563.4                     |

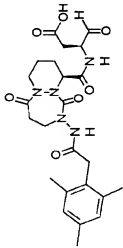
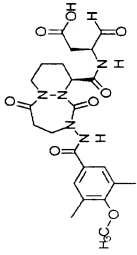
| Compound | Structure  | MF         | MW     | HPLC RT min<br>(method)<br>Purity | MS<br>(M+Na)+ |
|----------|--|------------|--------|-----------------------------------|---------------|
| 1116     |  | C23H25N5O9 | 515.48 | 14.144 (1)<br>85%                 | 538.8         |
| 1117     |  | C24H29N5O8 | 515.53 | 11.551 (2)<br>97%                 | 538.8         |

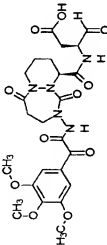
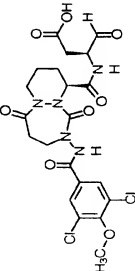


| Compound | Structure  | MF         | MW     | HPLC RT min<br>(method)<br>Purity | MS<br>(M+Na) + |
|----------|--|------------|--------|-----------------------------------|----------------|
| 1118     |  | C21H31N5O7 | 465.51 | 13.974 (1)<br>96%                 | 488.9          |
| 1119     |  | C22H33N5O7 | 479.54 | 11.079 (2)<br>95%                 | 502.9          |

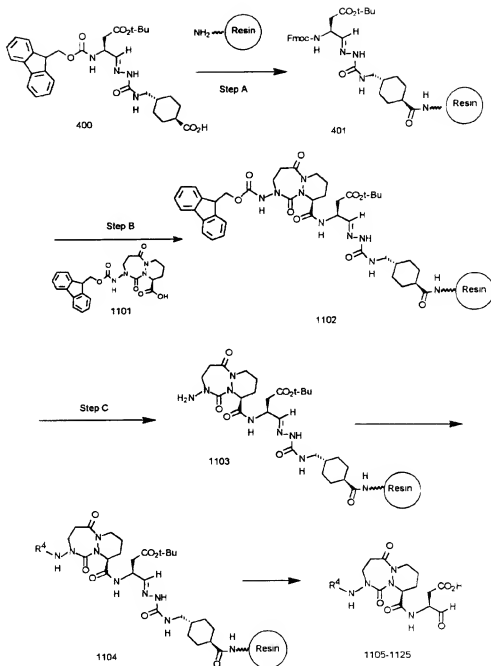
| Compound | Structure  | MF           | MW     | HPLC RT min<br>(method)<br>Purity | MS<br>(M+Na) + |
|----------|--|--------------|--------|-----------------------------------|----------------|
| 1120     |  | C21H23ClN6O8 | 522.91 | 16.796 (1)<br>99%                 | 547.3          |
| 1121     |  | C22H25N5O9   | 503.47 | 11.131 (1)<br>99%                 | 527.9          |

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| Compound | Structure  | MF          | MW     | HPLC RT min<br>(method)<br>Purity | MS<br>(M+Na) + |
|----------|--|-------------|--------|-----------------------------------|----------------|
| 1122     |  | C24H31N5O7  | 501.54 | 10.892 (2)<br>98%                 | 525.5          |
| 1123     |  | C26H24N4O10 | 552.50 | 15.85<br>>0.98                    | 574            |

| Compound | Structure  | MF  | MW     | HPLC RT min<br>(method)<br>Purity | MS<br>(M+Na)+ |
|----------|--|---|--------|-----------------------------------|---------------|
| 1124     |  | C <sub>24</sub> H <sub>29</sub> N <sub>5</sub> O <sub>11</sub>                | 563.53 | 13.336 (1)<br>99%                 | 587           |
| 1125     |  | C <sub>21</sub> H <sub>23</sub> Cl <sub>2</sub> N <sub>5</sub> O <sub>8</sub> | 544.35 | 8.99<br>0.95                      | 566           |

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**Step A. Synthesis of 401.** Tentagel S<sup>®</sup> NH<sub>2</sub> resin (0.25 mmol/g, 5.25 g) was placed in a sintered glass shaker vessel and washed with dimethylacetamide (3 X 15 mL). Compound 400 (1.36 g, 2.3 mmol) was

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dissolved in DMA (10 mL) and O-benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU; 0.88 g, 2.3 mmol), and DIEA (0.8 mL, 4.6 mmol) were added. The solution was transferred to the resin and a further 5 mL DMA added. The reaction mixture was agitated for 1.5 h at room temperature using a wrist arm shaker. The resin was filtered and washed with dimethylacetamide (4 X 15 mL).

**Step B. Synthesis of 1102.** Resin 401 was deprotected with 20% (v/v) piperidine/dimethylacetamide (15 mL) for 10 min (shaking) and then for 10 min with fresh piperidine reagent (15 mL). The resin was then washed with dimethylacetamide (6 X 15 mL), followed by N-methylpyrrolidone (2 X 25 mL). Compound 1101 (0.979 g, 2.11 mmol) was dissolved in dimethylacetamide (8 mL). HBTU (0.81 g, 2.1 mmol) and DIEA (0.75 mL, 4.3 mmol) were added and the solution added to the resin, followed by dimethylacetamide (4 mL). The reaction mixture was agitated for 2 h at room temperature using a wrist arm shaker. The resin work-up was performed as described for 401 to yield 1102.

**Step C. Synthesis of 1103.** This compound was prepared from resin 1102 (0.040 mmol) using an Advanced ChemTech 396 Multiple Peptide synthesizer. The automated cycles consisted of a resin wash with dimethylformamide (2 X 1 mL), deprotection with 25% (v/v) piperidine in dimethylformamide (1 mL) for 3 min followed by fresh reagent (1 mL) for 10 min to yield resin 1103. The resin was washed with

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dimethylformamide (3 X 1 mL) and N-methylpyrrolidone (3 X 1 mL).

Resin 1103 was acylated with a solution of 0.4M carboxylic acid and 0.4M HOBt in N-methylpyrrolidone (0.5 mL), a solution of 0.4M HBTU in N-methylpyrrolidone (0.5 mL) and a solution of 1.6M DIEA in N-methylpyrrolidone (0.25 mL) and the reaction was shaken for 2 hr at room temperature. The acylation step was repeated. Finally, the resin was washed with N-methylpyrrolidone (1 X 1 mL), dimethylformamide (4 X 1 mL), dichloromethane (5 X 1 mL) and dried *in vacuo*. The aldehyde was cleaved from the resin and globally deprotected by treatment with 95% TFA/ 5% H<sub>2</sub>O (v/v, 1.5 mL) for 30 min at room temperature. After washing the resin with cleavage reagent (1 mL), the combined filtrates were added to cold 1:1 ether:hexane (10 mL) and the resulting precipitate was isolated by centrifugation and decantation. The resulting pellet was dissolved in 10% acetonitrile/90% H<sub>2</sub>O/0.1% TFA (5 mL) and lyophilized to obtain crude 1105-1125 as a white powder. The compound was purified by semi-preparative RP-HPLC with a Rainin Microsorb™ C18 column (5 μ, 21.4 X 250 mm) eluting with a linear acetonitrile gradient (8% - 48%) containing 0.1% TFA (v/v) over 30 min at 12 mL/min. Fractions containing the desired product were pooled and lyophilized to provide 1105-1125 (10.8 mg, 63%).

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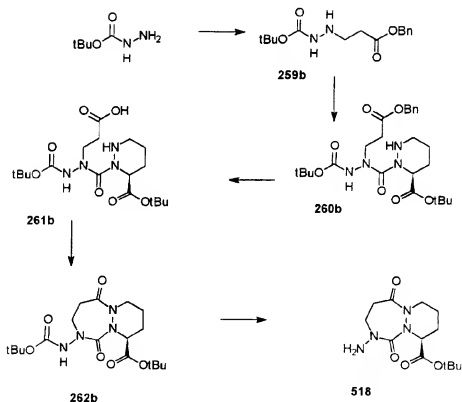
**Analytical HPLC methods:**

(1) Waters DeltaPak C18, 300Å (5μ, 3.9 X 150 mm).

Linear acetonitrile gradient (0% - 25%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.

5 (2) Waters DeltaPak C18, 300Å (5μ, 3.9 X 150 mm).

Linear acetonitrile gradient (5% - 45%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.

**Benzyl 3-(N'-t-butyloxycarbonylhydrazino)propionate****(259b)**, was synthesized via method used to prepare 259

10 from 258 to afford a waxy solid (87g, 51%): mp 54-55°C;

IR (film) 3324, 2978, 1732, 1713, 1455, 1367, 1277,



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1254, 1171;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.35 (5H, m), 6.15 (1H, bs),  
5.13 (2H, s), 3.15 (2H, t,  $J = 6.5$ ), 2.54 (2H, t,  $J =$   
6.5), 1.45 (9H, s). Anal. Calcd for  $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_3$ : C,  
61.21; H, 7.53; N, 9.52. Found: C, 61.29; H, 7.51; N,  
9.51. MS ( $\text{ES}^+$ ) 295 ( $\text{M}^+ + 1$ ).

(3S) 1-Benzyl 3-t-butyl 2-(N-2-benzyloxycarbonylethyl-  
NI-2-butoxycarbonylhydrazino)carbonyl  
hexahydropyridazine dicarboxylate (260b), was  
synthesized via method used to prepare 260 from 259 to  
afford a gum (81g) which was used in the next step  
without purification. Analytical data for a pure  
sample: IR (film) 3318, 2976, 1733, 1451, 1412, 1393,  
1366, 1256, 1161;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.34 (10H, m), 6.68  
(0.5H, bs), 5.11 (4H, m), 4.63 (0.5H, bs), 4.14 (1H,  
m), 3.53 (2H, m), 3.08 (1H, m), 2.63 (2H, m), 2.10-1.60  
(4H, m), 1.60-1.35 (19H, m + 2 x s).

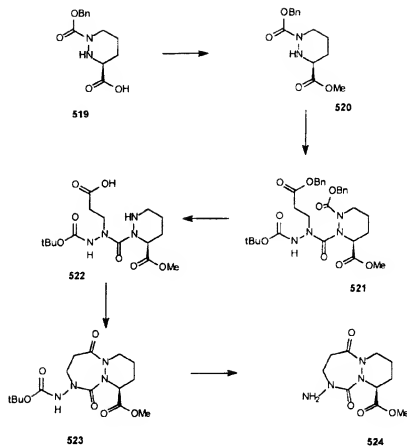
(3S) t-Butyl 2-(N'-t-butoxycarbonyl-N-2-  
carboxyethylhydrazino)-carbonylhexahydropyridazine 3-  
carboxylate (261b), was synthesized via method used to  
prepare 261 from 260 to give a gum which was purified  
by flash chromatography (1:1 ethyl  
acetate/dichloromethane) to give the title compound  
261b (36.0g, 79.4% over 2 stages): IR (film) 3267,  
2979, 2937, 1728, 1668, 1394, 1369, 1245, 1159;  $^1\text{H}$  NMR  
( $\text{CDCl}_3$ )  $\delta$  7.6 (1H, bs), 6.8 (1H, vbs), 4.47 (1H, bs),  
3.73 (2H, bs), 2.98 (1H, bs), 2.66 (3H, m), 2.04 (1H,  
bs), 1.84 (1H, m), 1.6-1.2 (21H, m + s).

(4S) t-Butyl 7-t-butoxycarbonylamino-6,10-dioxo-  
1,2,3,4,7,8,9,10-octahydro-6H-

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- pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (262b), was synthesized via method used to prepare 262 from 261 to give the title compound 262b, (18.6g, 54%) as an oil:  $[\alpha]_D^{20} +47.7^\circ$  (c 0.236,  $\text{CH}_2\text{Cl}_2$ ); IR (film) 3291, 2978, 1738, 1727, 1690, 1678, 1439, 1243, 1164;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  6.59 (1H, s), 5.06 (1H, m), 4.47 (1H, m), 3.85 (3H, m), 2.82 (1H, m), 2.37 (1H, m), 2.22 (1H, m), 1.92 (1H, m), 1.63 (2H, m), 1.48 and 1.46 (18H, 2 x s). MS ( $\text{ES}^+$ ) 399 ( $\text{M}^+ + 1$ ).
- 10 (4S) t-Butyl 7-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (518). Compound 262b (2.43g, 6.1mmol) was dissolved in 1M hydrogen chloride in ethyl acetate (30ml) and stirred at room temperature for 20h. Solid sodium bicarbonate (4g, 46.5mmol) and water 20ml were added and the mixture stirred for 5min before separating and extracting the aqueous portion with ethyl acetate. The combined organic solution was washed with water, saturated salt, dried ( $\text{MgSO}_4$ ) and concentrated. Purification by flash chromatography (50% ethyl acetate in dichloromethane - 100% ethyl acetate) gave the pure product 518 (1.08g, 59%) as an unstable oil:  $[\alpha]_D^{20} +82^\circ$  (c 0.55,  $\text{CH}_2\text{Cl}_2$ ); IR (film) 3331, 2977, 1731, 1680, 1664, 1439, 1420, 1315, 1158;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  5.08 (1H, m), 4.48 (1H, m), 3.80 (2H, Abq', 3.70 (2H, bs, exch with  $\text{D}_2\text{O}$ ), 3.53 (1H, m), 2.75 (1H, m), 2.30 (2H, m), 1.88 (1H, m), 1.71 (2H, m), 1.47 (9H, s).

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(3S) Methyl 1-benzyloxycarbonyl-hexahydropyridazine-3-carboxylate (520). 519 (9.4g, 35.6mmol) was suspended in methanol (230ml) and cooled to 0°C in an ice bath. Thionyl chloride (3ml, 4.89g, 41.1mmol) was added dropwise over 30min and the mixture stirred at ambient temperature for 48h. The solvent was removed in vacuo at 30°C and the oily residue dissolved in ethyl acetate (500ml). The organic solution was washed with saturated sodium bicarbonate, water and brine, dried (MgSO<sub>4</sub>) and concentrated to give 520 (7.84g, 79%) as an oil:  $[\alpha]_D^{22}$  -25.9° (c 0.615, CH<sub>2</sub>Cl<sub>2</sub>); IR (film) 2953, 1739, 1703, 1694, 1440, 1403, 1357, 1261, 1241, 1174; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.36 (5H, s), 5.18 (2H, s), 4.00 (1H,

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bd), 3.73 (3H, s), 3.55 (1H, dd), 3.12 (1H, t), 2.06 (1H, m), 1.73 (3H, m). Anal. Calcd for  $C_{14}H_{17}N_2O_4 \cdot 0.25H_2O$ : C, 59.46; H, 6.59; N, 9.91. Found: C, 59.44; H, 6.46; N, 10.09.

- 5 (3S) 1-Benzyl 3-methyl 2-(N-2-benzyloxycarbonylethyl-NI-t-butoxycarbonylhydrazino)carbonyl hexahydropyridazine dicarboxylate (521). Using a similar method to that described for 260 above, 521 was prepared, 96% as a crude oil:  $[\alpha]_D^{22} -22.16^\circ$  (c 0.25,  $CH_2Cl_2$ ); IR (film) 3316, 2976, 2953, 1738, 1726, 1714, 1690, 1367, 1260, 1167;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.25 (10H, m), 6.82 (1H, bs), 5.10 (4H, m), 4.80 (1H, bs), 4.3-3.4 (6H, m), 3.10 (1H, m), 2.59 (2H, m), 1.95 (2H, m), 1.44 (10H, m + s).
- 15 (3S) Methyl 2-(N'-t-butoxycarbonyl-N-2-carboxyethylhydrazino)-carbonyl hexahydropyridazine 3-carboxylate (522). Using a similar method to that described for 261 above, 522 was prepared, 92% as a white solid: mp. 146-148°C (decomp);  $[\alpha]_D^{22} +27.8^\circ$  (c 0.25,  $CH_2Cl_2$ ); IR (KBr) 3346, 1740, 1710, 1626, 1497, 1290, 1250, 1206, 1179, 1159;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.60 (1H, bs), 7.5-5.5 (1H, vbs), 4.64 (1H, bs), 3.76 (5H, m + s), 3.00 (1H, m), 2.70 (3H, m), 2.16 (1H, m), 1.92 (1H, m), 1.56 (1H, m), 1.46 (11H, m + s). Anal. Calcd for  $C_{15}H_{26}N_4O_7$ : C, 48.12; H, 7.00; N, 14.96. Found: C, 48.21; H, 6.96; N, 14.86. MS ( $ES^+$ ) 373 ( $M^+ - 1$ ).
- (4S) Methyl 7-t-butoxycarbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (523).

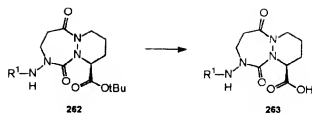
- 655 -

522 (7.15g, 19.1mmol) was dissolved in dichloromethane(100ml), containing dimethylformamide (0.5ml), and cooled to 0°C. Thionyl chloride (1.6ml, 2.61g, 22mmol) and N-ethyl morpholine (4.86ml, 440mg, 38.2mmol) were added and the mixture stirred for 2h. The organic mixture was washed with 2M sodium bisulphate (50ml), saturated sodium bicarbonate (50ml) and brine (50ml), dried (MgSO<sub>4</sub>) and concentrated. The residues were triturated with ether to give 523 as a white solid (5.73g, 84%): mp. 186-188°C (decomp);  $[\alpha]_D^{22} +65.3^\circ$  (c 0.25, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3298, 2978, 1750, 1720, 1682, 1658, 1455, 1423, 1369, 1316, 1241, 1212, 1160; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 6.56 (1H, s), 5.17 (1H, dd), 4.48 (1H, bd), 3.81 (3H, m), 3.75 (3H, s), 2.83 (1H, dt), 2.40 (1H, m), 2.28 (1H, m), 1.95 (1H, m), 1.67 (1H, m), 1.47 (9H, s). Anal. Calcd for C<sub>15</sub>H<sub>24</sub>N<sub>4</sub>O<sub>6</sub>•1/6H<sub>2</sub>O: C, 50.13; H, 6.82; N, 15.59. Found: C, 50.12; H, 6.71; N, 15.58. MS (ES<sup>+</sup>) 357 (M<sup>+</sup> - 1, 46%), 301 (100%).

(4S) Methyl 7-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (524), was synthesized from 523 via method used to prepare 518.

Compounds 262a-k were synthesized via methods used to prepare 211b-f.

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
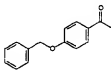
262a-k

263a-k

| compound     | R |
|--------------|---|
| 262a<br>263a |   |
| 262b<br>263b |   |
| 262c<br>263c |   |
| 262d<br>263d |   |
| 262e<br>263e |   |
| 262f<br>263f |   |
| 262g<br>263g |   |
| 262h<br>263h |   |

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|              |   |
|--------------|---|
| 262i<br>263i |  |
| 262j<br>263j | PhSO <sub>2</sub> —   |
| 262k<br>263k |  |

- 25 (4S) t-Butyl 6,10-dioxo-7-(2-naphthyl) sulfonamide-  
1,2,3,4,7,8,9,10-octahydro-6H-  
pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate  
(262a). 443mg (91%) of the title compound was  
obtained: mp. 56-7°C;  $[\alpha]_D^{25} +76^\circ$  (c 0.15, CH<sub>2</sub>Cl<sub>2</sub>); IR  
30 (KBr) 3429, 2979, 1734, 1675, 1418, 1369, 1339, 1323,  
1244, 1164, 665; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  8.45 (1H, s), 8.00-7.59  
(7H, m), 4.69-4.65 (1H, m), 4.25-4.12 (1H, m), 4.10-  
3.99 (1H, m), 3.73-3.55 (2H, m), 2.40-2.30 (1H, m),  
1.99-1.91 (1H, m), 1.82-1.62 (2H, m), 1.48-1.46 (2H,  
35 m), 1.37 (9H, s). Anal. Calcd for C<sub>23</sub>H<sub>28</sub>N<sub>4</sub>O<sub>6</sub>S•H<sub>2</sub>O: C,  
54.53; H, 5.97; N, 11.06. Found: C, 54.60; H, 5.73; N,  
10.95. MS (ES<sup>+</sup>) 489.

- (4S) t-Butyl 6,10-dioxo-7-(3-methoxyphenylureido)-  
1,2,3,4,7,8,9,10-octahydro-6H-  
40 pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate  
(262c), 120mg (80%) of colourless foam was obtained:

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$[\alpha]_D^{22} +22.6^\circ$  (c 0.1,  $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3316, 1732, 1671, 1609, 1551, 1495, 1455, 1432, 1316, 1288, 1245, 1218, 1158, 1122, 1023;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.16 (4H, m), 6.79 (1H, m), 6.60 (1H, m), 5.11 (1H, m), 4.59 (1H, m), 3.89 (2H, m), 3.77 (3H, s), 3.72 (2H, m), 2.85 (1H, m).

(4S) t-Butyl 6,10-dioxo-7-(2-methoxyphenylureido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino

[1,2-a][1,2,4]triazepine-4-carboxylate (262d), (81%)

was obtained as colourless foam:  $[\alpha]_D^{22} +3.7^\circ$  (c 0.1,

$\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3468, 3446, 3269, 1734, 1698, 1667, 1609, 1555, 1490, 1461, 1433, 1423, 1296, 1246, 1215, 1173, 1157, 1028, 756;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.23 (1H, m), 7.95 (1H, s), 6.95 (4H, m), 5.15 (1H, m), 4.60 (1H, m), 3.98-3.65 (4H, m), 3.89 (3H, s), 2.90 (1H, m), 2.48 (1H, m), 2.25 (1H, m), 2.05-1.65 (2H, m), 1.48 (9H, s).

(4S) t-Butyl 6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylacetyl-amino-6H-

pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate

(262e), was obtained as a white foamy solid (155mg,

53%): mp.  $53-7^\circ\text{C}$ ;  $[\alpha]_D^{22} +57.4^\circ$  (c 0.1,  $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3271, 2978, 1733, 1680, 1437, 1314, 1245, 1156;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.46 (1H, s), 7.42-7.20 (5H, m), 5.03 (1H, dd), 4.52-4.40 (1H, m), 3.96-3.70 (2H, m), 3.70-3.49 (1H, m), 3.63 (2H, s), 2.92-2.75 (1H, m), 2.43-2.33 (1H, m), 2.33-2.15 (1H, m), 2.00-1.50 (3H, m), 1.45 (9H, s). Anal. Calcd for  $\text{C}_{21}\text{H}_{28}\text{N}_4\text{O}_5 \cdot 0.25\text{H}_2\text{O}$ : C, 59.91; H, 6.82; N, 13.31. Found: C, 60.19; H, 6.60; N, 13.30. MS ( $\text{ES}^+$ ) 418 ( $\text{M}^+ + 2$ , 25%), 417 ( $\text{M}^+ + 1$ , 100), 362 (9), 361 (45).



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- (4S) t-Butyl 6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-7-(3-phenylureido)-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (262f), was obtained as a white solid (273mg, 93%): mp. 102-6°C;  $[\alpha]_D^{22} +7.5^\circ$  (c 0.07, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3320, 2979, 1731, 1676, 1669, 1601, 1549, 1444, 1314, 1240, 1156; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.37-7.20 (6H, m), 7.08-6.98 (1H, m), 5.12 (1H, dd), 4.64-4.55 (1H, m), 4.02-3.78 (2H, m), 3.75-3.65 (1H, m), 2.94-2.75 (1H, m), 2.57-2.35 (1H, m), 2.35-2.20 (1H, m), 2.00-1.50 (3H, m), 1.48 (9H, s). Anal. Calcd for C<sub>20</sub>H<sub>27</sub>N<sub>5</sub>O<sub>5</sub>•0.4H<sub>2</sub>O: C, 56.56; H, 6.60; N, 16.49. Found: C, 56.89; H, 6.58; N, 16.07. MS (ES<sup>+</sup>) 419 (M<sup>+</sup> + 2, 24%), 418 (M<sup>+</sup> + 1, 100), 363 (15), 362 (81), 242 (10).

- (4S) t-Butyl 6,10-dioxo-7-(indole-2-carboxamido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (262g), (13g) was obtained as a white solid (298mg, 70%): mp. 138-43°C;  $[\alpha]_D^{23} +69.8^\circ$  (c 0.1, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3282, 2978, 1733, 1664, 1536, 1421, 1310, 1156, 748; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.67 (1H, s), 9.53 (1H, s), 7.50 (1H, d), 7.30-7.15 (2H, m), 7.10-7.00 (1H, m), 6.93 (1H, s), 5.16-5.12 (1H, m), 4.60-4.50 (1H, m), 4.05-3.85 (2H, m), 3.85-3.70 (1H, m), 3.05-2.90 (1H, m), 2.55-2.35 (1H, m), 2.35-2.20 (1H, m), 2.00-1.85 (1H, m), 1.85-1.50 (2H, m), 1.47 (9H, s). Anal. Calcd for C<sub>22</sub>H<sub>27</sub>N<sub>5</sub>O<sub>5</sub>•0.45H<sub>2</sub>O: C, 58.77; H, 6.26; N, 15.58. Found: C, 59.14; H, 6.24; N, 15.18. MS (ES<sup>+</sup>) 433 (M<sup>+</sup> + 2, 26%), 442 (M<sup>+</sup> + 1, 100), 387 (17), 386 (79), 285 (20), 229 (85), 211 (26), 185 (15), 183 (57), 139 (9).

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(4S) t-Butyl 7-[(4-acetamido)benzamido]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]-triazepine-4-carboxylate (262h), was obtained as a white solid (325mg, 73%): mp. 209-12°C;  $[\alpha]_D^{24} +62.4^\circ$  (c 0.2, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3513, 3269, 2980, 1731, 1680, 1653, 1599, 1531, 1314, 1158; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.40 (1H, s), 8.75 (1H, s), 7.72 (2H, d), 7.47 (2H, d), 5.15-5.05 (1H, m), 4.55-4.45 (1H, m), 4.05-3.70 (3H, m), 3.00-2.80 (1H, m), 2.45-2.35 (1H, m), 2.30-2.15 (1H, m), 2.10 (3H, s), 2.00-1.80 (1H, m), 1.80-1.50 (2H, m), 1.48 (9H, s). Anal. Calcd for C<sub>22</sub>H<sub>29</sub>N<sub>5</sub>O<sub>6</sub>: C, 57.51; H, 6.36; N, 15.24. Found: C, 57.41; H, 6.38; N, 15.12. MS (ES<sup>+</sup>) 461 (M<sup>+</sup> + 2, 26%), 460 (M<sup>+</sup> + 1, 100), 405 (12), 404 (55), 354 (7), 285 (23), 229 (52), 183 (22).

15 (4S) t-Butyl 6,10-dioxo-7-(4-methoxybenzoylamino)-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-carboxylate (262i), was obtained as a white glassy solid (76%): mp. 85-9°C;  $[\alpha]_D^{25} +66.4^\circ$  (c 0.11, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 1732, 1668, 1607, 1502, 1440, 1312, 1295, 1258, 1176, 1157, 1025; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.25 (1H, s), 7.77 (2H, m), 6.90 (2H, m), 5.11-5.07 (1H, m), 4.55-4.48 (1H, m), 4.01-3.91 (2H, m), 3.86-3.78 (1H, m), 3.85 (3H, s), 2.98 (1H, m), 2.46-2.40 (1H, m), 2.26-2.20 (1H, m), 2.05-1.80 (1H, m), 1.70-1.64 (2H, m), 1.48 (9H, s).

(4S) t-Butyl 6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylsulphonylamino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (262j), was obtained as a white crystalline solid (79%): mp. 182-3°C (dec);  $[\alpha]_D^{22} +92.1^\circ$  (c 0.4, CH<sub>2</sub>Cl<sub>2</sub>);

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IR (KBr) 3283, 1732, 1684, 1448, 1430, 1404, 1369, 1338, 1306, 1285, 1242, 1169, 1091, 692;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.89 (2H, d,  $J = 7.4$ ), 7.76 (1H, s), 7.64-7.49 (3H, m), 4.83 (1H, m), 4.35 (1H, brd,  $J = 13.0$ ), 4.00 (1H, m), 3.74-3.63 (2H, m), 2.39-2.26 (2H, m), 2.06 (1H, m), 1.50-1.41 (10H, m). Anal. Calcd for  $\text{C}_{19}\text{H}_{26}\text{N}_4\text{O}_6$ : C, 52.04; H, 5.98; N, 12.78. Found: C, 52.11; H, 5.95; N, 12.71. MS ( $\text{ES}^+$ ) 437 ( $\text{M}^+ - 1$ , 100%).

(3S) t-Butyl (7-(4-benzyloxyphenyl)carbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino [1,2-a][1,2,4]triazepine-4-carboxylate (262k), (83%) was obtained:  $[\alpha]_{\text{D}}^{22} +42.3^\circ$  (c 0.11,  $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3287, 2997, 2935, 1735, 1681, 1606, 1501, 1296, 1248, 1173, 1155.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  9.23 (1H, s), 7.73 (2H, d), 7.38 (5H, m), 6.85 (2H, d), 5.08 (1H, m), 5.02 (2H, s), 4.48 (1H, bd), 4.15-3.65 (3H, m), 2.96 (1H, m), 2.45-2.10 (2H, m), 1.88 (1H, m), 1.63 (2H, m), 1.48 (9H, s). M.S. ( $\text{ES}^+$ ) 509 ( $\text{M}^+ + 1$ ).

Compounds 263a-k were synthesized via methods used to prepare 212b-f.

(4S) 6,10-Dioxo-7-(2-naphthalenesulfonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid (263a), 348mg (94%) obtained as a white foamy solid: mp.  $[\alpha]_{\text{D}}^{21} +171^\circ$  (c 0.056,  $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3426, 3233, 2953, 1734, 1663, 1481, 1415, 1340, 1214, 1167, 1132, 1075, 668;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.44 (1H, s), 8.00-7.60 (7H, m), 4.85-4.83 (1H, m), 4.25-4.00 (1H, m), 4.07-3.90 (1H, m), 3.70-3.46 (2H, m), 2.38-2.30 (1H, m), 2.12-

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2.01 (1H, m), 1.91-1.83 (1H, m), 1.46-1.26 (1H, m),  
1.13-1.06 (1H, m), 0.90-0.77 (1H, m). MS (ES<sup>+</sup>) 431.

(4S) 7-(Benzo[b]thiophene-2-carbonyl)amino-6,10-dioxo-  
1,2,3,4,7,8,9,10-octahydro-6H-

- 5 pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid  
(263b). 200mg (100%) was obtained as a white solid:  
mp. 155°C;  $[\alpha]_D^{20} +13^\circ$  (c 0.07, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3431,  
2935, 1734, 1663, 1531, 1435, 1292, 1177; <sup>1</sup>H NMR  
(CDCl<sub>3</sub>)  $\delta$  9.73 (1H, bs), 7.73-7.27 (5H, m), 5.35-5.25  
10 (1H, m), 4.56-4.48 (1H, m), 4.05-3.65 (3H, m), 3.12-  
3.00 (1H, m), 2.50-2.45 (1H, m), 2.30-2.20 (1H, m),  
2.10-2.00 (1H, m), 1.75-1.61 (2H, m). MS (ES<sup>+</sup>) 401.

(4S) 6,10-Dioxo-7-(3-methoxyphenylureido)-  
1,2,3,4,7,8,9,10-octahydro-6H-

- 15 pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid  
(263c), 216mg, (100%) obtained as a colourless foam:  
 $[\alpha]_D^{23} 32.5^\circ$  (c 0.1, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3326, 1730,  
1661, 1610, 1555, 1495, 1431, 1314, 1288, 1217, 1175,  
1161; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.87 (1H, s), 7.58 (1H, s), 7.19  
20 (2H, m), 6.82 (1H, m), 6.62 (1H, m), 5.21 (1H, m), 4.55  
(1H, m), 3.76 (3H, s), 4.0-3.65 (4H, m), 2.85 (1H, m),  
2.35 (2H, m), 1.75 (1H, m), 1.71 (2H, m).

(4S) 6,10-Dioxo-7-(2-methoxyphenylureido)-  
1,2,3,4,7,8,9,10-octahydro-6H-

- 25 pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid  
(263d), (100%) obtained as colourless foam:  $[\alpha]_D^{24}$   
+11.7° (c 0.1, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3394, 3325, 1666,  
1603, 1543, 1490, 1463, 1438, 1329, 1311, 1292, 1249,  
1214, 1176, 1119, 1024, 752; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  8.15 (1H,

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m), 7.97 (2H, m), 7.15-6.84 (3H, m), 5.29 (1H, m), 4.62 (1H, m), 4.04-3.65 (4H, m), 3.89 (3H, s), 2.92 (1H, m), 2.50 (1H, m), 2.30 (1H, m), 2.10-1.75 (2H, m).

**(4S) 6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-7-**

**5 phenylacetyl-amino-6H-**

**pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid**

**(263e)**, obtained as a white foamy solid (117mg, 98%):

mp. 109-14°C;  $[\alpha]_D^{24} +82.6^\circ$  (c 0.06, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3700-2250 (br), 3437, 3274, 2959, 1733, 1664, 1481,

10 1437, 1310, 1177; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.99 (1H, s), 7.40-7.15 (5H, m), 5.15-5.10 (1H, m), 5.25-4.70 (1H, bs), 4.50-4.35 (1H, m), 3.95-3.50 (3H, m), 3.61 (2H, s), 2.93-2.78 (1H, m), 2.40-2.20 (2H, m), 2.10-1.80 (1H, m), 1.80-1.60 (2H, m). Anal. Calcd for C<sub>17</sub>H<sub>20</sub>N<sub>4</sub>O<sub>5</sub>·1H<sub>2</sub>O:

15 C, 53.96; H, 5.86; N, 14.81. Found: C, 54.12; H, 5.50; N, 14.68. MS (ES<sup>+</sup>) 360 (M<sup>+</sup>, 21%), 359 (M<sup>+</sup> - 1, 100), 196 (14), 182 (14), 111 (7).

**(4S) 6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-7-(3-**

**phenylureido)-6H-pyridazino[1,2-a][1,2,4]triazepine-4-**

**20 carboxylic acid (263f)**, obtained as a white foamy solid

(199mg, 92%): mp. 149-52°C;  $[\alpha]_D^{24} +92.0^\circ$  (c 0.01, CH<sub>3</sub>OH); IR (KBr) 3700-2300 (br), 3319, 2956, 1726, 1664, 1600, 1548, 1500, 1444, 1313, 1238, 755; <sup>1</sup>H NMR

(D<sub>6</sub>-DMSO) δ 8.90 (1H, s), 8.24 (1H, s), 7.42 (2H, d),

25 7.30-7.20 (2H, m), 7.00-6.90 (1H, m), 4.98-4.92 (1H, m), 4.32-4.22 (1H, m), 3.80-3.55 (3H, m), 2.85-2.70 (1H, m), 2.30-2.20 (1H, m), 2.20-2.00 (1H, m), 1.90-1.35 (3H, m). Anal. Calcd for C<sub>16</sub>H<sub>19</sub>N<sub>5</sub>O<sub>5</sub>·0.75H<sub>2</sub>O: C, 51.26; H, 5.51; N, 18.68. Found: C, 51.11; H, 5.23; N,

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18.42. MS ( $\text{ES}^+$ ) 361 ( $\text{M}^+$ , 20%), 360 ( $\text{M}^+ - 1$ , 100), 241 (11), 240 (89), 196 (15), 175 (29), 111 (12).

(4S) 6,10-Dioxo-7-(indole-2-carboxamido)-  
1,2,3,4,7,8,9,10-octahydro-6H-

- 5 pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid (263g), was obtained as a white solid (259mg, 92%)mp. 248-51°C;  $[\alpha]_{\text{D}}^{24} +94.0^\circ$  (c 0.01,  $\text{CH}_3\text{OH}$ ); IR (KBr) 3700-2300 (br) 3341, 2956, 1738, 1668, 1651, 1529, 1425, 1311, 1259, 751;  $^1\text{H}$  NMR ( $\text{D}_6$ -DMSO)  $\delta$  13.29 (1H, bs),  
10 11.72 (1H, s), 10.64 (1H, s), 7.65 (1H, d), 7.45 (1H, d), 7.26-7.15 (1H, m), 7.17 (1H, s), 7.10-7.00 (1H, m), 5.05-4.95 (1H, m), 4.40-4.25 (1H, m), 3.90-3.50 (3H, m), 2.88-2.75 (1H, m), 2.38-2.20 (1H, m), 2.20-2.00 (1H, m), 1.90-1.35 (3H). Anal. Calcd for  
15  $\text{C}_{18}\text{H}_{19}\text{N}_5\text{O}_5 \cdot 0.5\text{H}_2\text{O}$ : C, 53.59; H, 5.25; N, 17.35. Found: C, 53.66; H, 4.88; N, 17.11. MS ( $\text{ES}^+$ ) 385 ( $\text{M}^+$ , 23%), 384 ( $\text{M}^+ - 1$ , 100), 298 (6), 253 (8), 227 (10), 199 (23), 196 (10), 173 (9), 126 (21).

(4S) 7-[(4-Acetamido)benzamido]-6,10-dioxo-

- 20 1,2,3,4,7,8,9,10-octahydro-6H-  
pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid (263h), was obtained as a white solid (282mg, 99%): mp. 210-5°C;  $[\alpha]_{\text{D}}^{24} +74.5^\circ$  (c 0.01,  $\text{CH}_3\text{OH}$ ); IR (KBr) 3700-2300 (br) 3444, 3316, 2960, 1664, 1599, 1531, 1439,  
25 1301, 1184;  $^1\text{H}$  NMR ( $\text{D}_6$ -DMSO)  $\delta$  13.30 (1H, bs), 10.50 (1H, s), 10.25 (1H, s), 7.80 (2H, d), 7.68 (2H, d), 5.00-4.90 (1H, m), 4.35-4.25 (1H, m), 3.90-3.40 (3H, m), 2.88-2.70 (1H, m), 2.35-2.25 (1H, m), 2.25-1.95 (1H, m), 2.08 (3H, s), 1.95-1.35 (3H, m). MS ( $\text{ES}^+$ ) 403

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(M<sup>+</sup>, 10%), 402 (M<sup>+</sup> - 1, 100), 358 (10), 247 (10), 227 (16), 219 (51), 198 (12), 184 (17).

**(4S) 6,10-Dioxo-7-(4-methoxybenzoylamino)-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-carboxylic acid**

- 5 (263i), was obtained as a white glassy solid (approx 100%) used without purification: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.23 (1H, s), 7.72 (2H, d, J = 8.8), 6.81 (2H, d, J = 8.9), 5.22 (1H, m), 4.51 (1H, m), 3.97-3.72 (2H, m), 3.81 (3H, s), 3.03 (1H, m), 2.51-2.46 (1H, m), 2.31-2.25  
10 (1H, m), 2.03 (1H, m), 1.72 (2H, m).

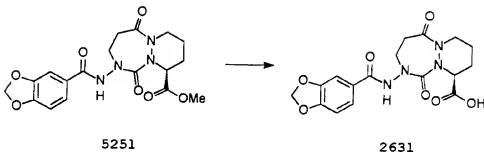
**(4S) 6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylsulphonylamino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid**

- (263j), was obtained as a white solid (100%): mp. 73-  
15 83°C (dec); [α]<sub>D</sub><sup>22</sup> +104.7° (c 0.3, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3600-2500 (br), 3208, 1734, 1666, 1481, 1446, 1416, 1338, 1311, 1214, 1171, 1091, 729, 689; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.87 (3H, m), 7.70-7.50 (3H, m), 7.16 (1H, brs), 4.99 (1H, m), 4.37 (1H, brd, J = 12.8), 3.92 (1H, m), 3.67  
20 (2H, m), 2.36 (2H, m), 2.13 (1H, brd, J = 12.2), 1.56 (3H, m). Anal. Calcd for C<sub>15</sub>H<sub>18</sub>SN<sub>4</sub>O<sub>6</sub>•0.25CF<sub>3</sub>CO<sub>2</sub>H: C, 45.31; H, 4.48 N, 13.64. Found: C, 45.48; H, 4.71; N, 13.43. MS (ES<sup>+</sup>) 383 (MH<sup>+</sup>, 100%). Accurate mass calculated for C<sub>15</sub>H<sub>19</sub>SN<sub>4</sub>O<sub>6</sub> (MH<sup>+</sup>): 383.1025. Found:  
25 383.1007.

**(4S) 7-(4-Benzoyloxyphenyl)carbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid**  
(263k), (100%) obtained: mp. 130-142°C; IR (KBr) 3272,

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2945, 1738, 1650, 1611, 1501, 1445, 1309, 1255, 1171;  
<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.35 (1H, s), 7.74 (2H, d), 7.38 (5H, m), 6.85 (2H, d), 5.40 (1H, bs), 5.19 (1H, s), 5.02 (2H, s), 4.49 (1H, d), 3.92 (2H, m), 3.68 (1H, m), 2.99  
 5 (1H, bs), 2.43 (1H, bs), 2.22 (1H, bs), 1.99 (1H, bs), 1.68 (2H, bs).



- (4S) Methyl 6,10-dioxo-7-(3,4-methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (5251), was synthesized via method used to prepare 211 to afford a white crystalline solid (3.35g, 83%): mp. 214-5°C; [α]<sub>D</sub><sup>20</sup> +75.2° (c 0.1, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3272, 2955, 1747, 1664, 1610, 1485, 1443, 1265, 1040; <sup>1</sup>H NMR  
 15 (CDCl<sub>3</sub>) δ 8.66 (1H, s), 7.32 (1H, dd), 7.23 (1H, d), 6.76 (1H, d), 6.02 (2H, s), 5.20 (1H, dd), 4.55-4.45 (1H, m), 4.03-3.70 (3H, m), 3.78 (3H, s), 3.05-2.88 (1H, m), 2.47-2.35 (1H, m), 2.35-2.20 (1H, m), 2.10-1.90 (1H, m), 1.85-1.50 (2H, m). Anal. Calcd for  
 20 C<sub>18</sub>H<sub>20</sub>N<sub>4</sub>O<sub>7</sub>·0.5H<sub>2</sub>O: C, 52.87; H, 5.06; N, 13.70. Found: C, 52.84; H, 5.00; N, 13.66. MS (ES<sup>+</sup>) 406 (M<sup>+</sup> + 2, 20%), 405 (M<sup>+</sup> + 1, 100), 391 (10), 162 (6), 148 (3), 105 (2).

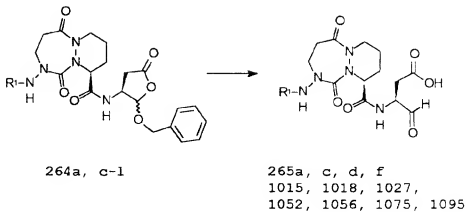
(4S) 6,10-Dioxo-7-(3,4-methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6H-



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pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid (2631). A suspension of 5251 (3.32g, 8.2mmol) in tetrahydrofuran (60ml) was treated with a solution of LiOH·H<sub>2</sub>O (0.69g, 16.4mmol, 2.0 equiv) in water (20ml).

5 The resulting mixture was stirred for 1h, concentrated and the residue dissolved in water (50ml). The solution was acidified using 2M.  $\text{NaHSO}_4$  and the product extracted with EtOAc (100ml and 50ml portions). The combined extract was washed once with brine (2 x 50ml),  
10 dried ( $\text{MgSO}_4$ ) and concentrated to afford **2631** as a white crystalline solid (2.87g, 90%): mp. 154-8°C;  $[\alpha]_D^{20} +85.6^\circ$  (c 0.01,  $\text{CH}_3\text{OH}$ ); IR (KBr) 3700-2300 (br), 3248, 2942, 1733, 1681, 1658, 1648, 1536, 1486, 1440, 1297, 1255, 1037;  $^1\text{H}$  NMR ( $\text{D}_6$ -DMSO)  $\delta$  13.23 (1H, bs),  
15 10.45 (1H, s), 7.45 (1H, d), 7.35 (1H, s), 7.03 (1H, d), 6.12 (2H, s), 5.00-4.93 (1H, m), 4.35-4.25 (1H, m), 3.90-3.40 (3H, m), 2.95-2.70 (1H, m), 2.40-2.25 (1H, m), 2.15-2.00 (1H, m), 1.91-1.40 (3H, m). Anal. Calcd for  $\text{C}_{17}\text{H}_{18}\text{N}_4\text{O}_7 \cdot 0.8\text{H}_2\text{O}$ : C, 50.45; H, 4.88; N, 13.84.  
20 Found: C, 50.80; H, 4.95; N, 13.36. MS ( $\text{ES}^+$ ) 390 ( $\text{M}^+$ , 19%), 389 ( $\text{M}^+ - 1$ , 100), 345 (9), 264 (31), 182 (27), 111 (12).



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| compound     | R <sup>1</sup> |
|--------------|----------------|
| 264a<br>265a |                |
| 264c<br>265c |                |
| 264d<br>265d |                |
| 264e<br>1095 |                |
| 264f<br>265f |                |
| 264g<br>1075 |                |
| 264h<br>1018 |                |
| 264i<br>1052 |                |
| 264j<br>1027 |                |



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|                            |   |
|----------------------------|---|
| <b>264k</b><br><b>1056</b> |  |
| <b>264l</b><br><b>1015</b> |  |

[4*S*(2*S*,3*S*)] *N*-(2-Benzoyloxy-5-oxo-tetrahydrofuran-3-yl)-  
 25 6,10-dioxo-7-(2-naphthalenesulfonyl)amino-  
 1,2,3,4,7,8,9,10-octahydro-6*H*-  
 pyridazino[1,2-*a*][1,2,4]triazepine-4-carboxamide  
 (264*a*), was synthesized by a similar method as compound  
 213*e* to afford a white solid (240mg, 82%): IR (KBr)  
 30 3380, 3066, 2947, 1789, 1750, 1691, 1454, 1417, 1368,  
 1298, 1262, 1235, 1193, 1118, 756, 696; <sup>1</sup>H NMR (D<sub>6</sub>-  
 DMSO) δ 8.59 (1*H*, d, *J* = 6.8), 8.48 (1*H*, s), 8.25-8.09  
 (3*H*, m), 7.85-7.75 (3*H*, m), 7.36 (5*H*, m), 5.39 (1*H*, m),  
 4.21 (2*H*, AB, *J* = 14.2), 4.53-4.49 (1*H*, m), 4.25-4.10  
 35 (2*H*, m), 3.65-3.44 (3*H*, m), 3.13-2.99 (1*H*, m), 2.43-  
 2.16 (1*H*, m), 1.72-0.72 (7*H*, m). Anal. Calcd for  
 C<sub>30</sub>H<sub>31</sub>N<sub>5</sub>O<sub>8</sub>S: C, 57.96; H, 5.03; N, 11.27. Found: C,  
 57.28; H, 5.14; N, 10.48. MS (ES<sup>+</sup>) 622.

[4*S*(2*S*,3*S*)] *N*-(2-Benzoyloxy-5-oxo-tetrahydrofuran-3-yl)-  
 40 6,10-dioxo-7-(3-methoxyphenylureido)-1,2,3,4,7,8,9,10-  
 octahydro-6*H*-pyridazino[1,2-*a*][1,2,4]triazepine-1-  
 carboxamide (264*c*), was prepared by a similar method as  
 213*e*, (55%) as a colourless foam: mp. 135-40°C; [α]<sub>D</sub><sup>22</sup>  
 +51.6° (c 0.1, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3314, 1790, 1664,

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1608, 1543, 1496, 1455, 1428, 1325, 1287, 1250, 1218, 1160, 1118; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.00 (1H, d, J = 7.1), 7.66 (1H, s), 7.55 (1H, s), 7.28 (5H, m), 7.14 (2H, m), 6.87 (1H, d, J = 7.4), 6.59 (1H, m), 5.42 (1H, s), 4.66 (5H, m), 3.90-3.65 (4H, m), 3.73 (3H, s), 2.98 (2H, m), 2.38 (2H, m), 2.01-1.65 (3H, m).

[4*S*(2*S*,3*S*)] N-(2-Benzoyloxy-5-oxo-tetrahydrofuran-3-yl)-6,10-dioxo-7-(2-methoxyphenylureido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-1-carboxamide (264d), was prepared by a similar method as 213e, (72%) as colourless foam: [α]<sub>D</sub><sup>22</sup> +21.4° (c 0.1, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3302, 1791, 1689, 1678, 1664, 1602, 1536, 1489, 1461, 1437, 1420, 1249, 1119, 1023, 942, 751; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.07 (1H, d, J = 7.7), 7.82 (1H, s), 7.68 (1H, d, J = 6.7), 7.49 (1H, s), 7.34 (5H, m), 6.96 (3H, m), 5.47 (1H, s), 4.82 (2H, d + m, J = 11.5), 4.63 (1H, d, J = 11.5), 4.49 (2H, m), 3.85 (4H, s + m), 3.68 (2H, m), 3.01 (2H, m), 2.46 (2H, m), 1.95 (3H, m), 1.57 (1H, m).

[4*S*(2*RS*,3*S*)] N-(2-Benzoyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylacetyl-amino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide (264e) was synthesized via a similar method as used to prepare 213e to afford a mixture of diastereomers (Syn:anti isomer ratio 9:1) as a white glassy solid (128mg, 78%); mp. 103-8°C; IR (KBr) 3419, 3302, 1793, 1664, 1535, 1421, 1327, 1256, 1123, 973; <sup>1</sup>H NMR (D<sub>6</sub>-DMSO) δ 10.20 (0.9H, s), 9.35 (0.1H, s), 8.74 (0.1H, d), 8.49 (0.9H, d), 7.36-7.15 (10H, m), 5.67 (0.9H, d), 5.44 (0.1H, s),

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4.85-4.75 (1H, m), 4.74-4.60 (1H, m), 4.77 and 4.63 (2H, dd), 4.30-4.10 (1H, m), 3.80-3.40 (3H, m), 3.43 (2H, s), 3.10-2.40 (3H, m), 2.25-2.15 (1H, m), 2.00-1.35 (4H, m). Anal. Calcd for  $C_{28}H_{31}N_5O_7 \cdot 0.5H_2O$ : C, 60.21; H, 5.77; N, 12.53. Found: C, 60.38; H, 5.83; N, 12.13. MS ( $ES^+$ ) 551 ( $M^+ + 2$ , 33%), 550 ( $M^+ + 1$ , 100), 480 (7), 343 (8), 279 (4).

[4S(2RS,3S)] N-(2-Benzoyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-7-(3-phenylureido)-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide (264f), was prepared by a similar method as compound 213e to afford the pure syn-isomer as a white foamy solid (225mg, 82%): mp. 130-5°C;  $[\alpha]_D^{24} +10.8^\circ$  (c 0.1,  $CH_2Cl_2$ ); IR (KBr) 3316, 1791, 1688, 1676, 1664, 1601, 1536, 1445, 1314, 1242, 973;  $^1H$  NMR ( $D_6$ -DMSO)  $\delta$  8.84 (1H, s), 8.49 (1H, d), 8.19 (1H, s), 7.45-7.18 (9H, m), 7.00-6.90 (1H, m), 5.68 (1H, d), 4.90-4.81 (1H, m), 4.75-4.60 (1H, m), 4.78 and 4.63 (2H, dd), 4.30-4.20 (1H, m), 3.75-3.55 (3H, m), 2.85-2.55 (3H, m), 2.25-2.15 (1H, m), 2.00-1.35 (4H, m). Anal. Calcd for  $C_{27}H_{30}N_6O_7 \cdot 0.5H_2O$ : C, 57.95; H, 5.58; N, 15.02. Found: C, 58.12; H, 5.64; N, 14.81. MS ( $ES^+$ ) 552 ( $M^+ + 2$ , 30%), 551 ( $M^+ + 1$ , 100), 362 (19), 299 (10), 279 (4).

[4S(2S,3S)] N-(2-Benzoyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-7-(indole-2-carboxamido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide (264g), was prepared by a similar method as compound 213e to afford the pure anti-isomer as a white solid (284mg, 80%): mp. 148-53°C;  $[\alpha]_D^{24} +72.0^\circ$  (c 0.1,

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CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3404, 3295, 1789, 1660, 1536, 1421, 1310, 1260, 1122, 749; <sup>1</sup>H NMR (D<sub>6</sub>-DMSO) δ 11.72 (1H, s), 10.58 (1H, s), 8.73 (1H, d), 7.65 (1H, d), 7.58-7.27 (6H, m), 7.27-7.10 (1H, m), 7.17 (1H, s), 7.10-7.00 (1H, m), 5.46 (1H, s), 4.90-4.85 (1H, m), 4.77 and 4.68 (2H, dd), 4.35-4.25 (2H, m), 3.95-3.55 (3H, m), 3.09 (1H, dd), 2.95-2.80 (1H, m), 2.47-2.25 (2H, m), 2.10-1.35 (4H, m). MS (ES<sup>+</sup>) 574 (M<sup>+</sup>, 35%), 573 (M<sup>+</sup> - 1, 100), 384 (16), 383 (69), 341 (23), 327 (12), 267 (13), 200 (22).

[4S(2RS,3S)] 7-[(4-Acetamido)benzamido]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide (264h), was prepared by a similar method as compound 213e to afford a mixture of diastereomers (Syn:anti isomer ratio 9:1) as a white solid (276mg, 70%): mp. 147-52°C; IR (KBr) 3444, 3304, 1793, 1665, 1602, 1531, 1505, 1423, 1294, 1264, 1181, 1123, 966; <sup>1</sup>H NMR (D<sub>6</sub>-DMSO) δ 10.41 (1H, s), 10.22 (1H, s), 8.71 (0.1H, d), 8.48 (0.9H, d), 7.78 (2H, d), 7.67 (2H, d), 7.35-7.30 (5H, m), 5.68 (0.9H, d), 5.45 (0.1H, s), 4.89-4.80 (1H, m), 4.75-4.60 (1H, m), 4.77 and 4.63 (2H, dd), 4.30-4.20 (1H, m), 3.90-3.50 (3H, m), 3.10-2.50 (3H, m), 2.35-2.20 (1H, m), 2.07 (3H, s), 2.05-1.35 (4H, m). Anal. Calcd for C<sub>29</sub>H<sub>32</sub>N<sub>6</sub>O<sub>8</sub>·1H<sub>2</sub>O: C, 57.04; H, 5.61; N, 13.76. Found: C, 56.79; H, 5.50; N, 13.53. MS (ES<sup>+</sup>) 594 (M<sup>+</sup> + 2, 34%), 593 (M<sup>+</sup> + 1, 100), 387 (8), 386 (38), 358 (8), 162 (19).

[4S(2RS,3S)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-7-(4-methoxybenzoylamino)-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide

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- (264i), was prepared by a similar method to that described for compound **213e** to afford a white solid (70%): mp. 116-118°C; IR (KBr) 3315, 2951, 1793, 1664, 1607, 1502, 1258, 1177; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.07 (1H, s), 7.77 (2H, d, J = 8.6), 7.35 (5H, m), 6.94 (2H, d, J = 8.5), 6.74 (1H), 4.89 (1H, d, J = 11.1), 4.74 (1H, m), 4.60 (1H, d, J = 11.0), 4.48, 4.41 (1H, 2m), 3.86 (3H, s), 3.79, 3.71-3.53 (3H, 2m), 2.87 (2H, m), 2.44 (1H, m), 2.18, 1.91, 1.68 (5H, 3m).
- 10 **[4S(2S,3S)] N-(2-Benzylloxy-5-oxotetrahydrofuran-3-yl)6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylsulphonylamino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide (264j)**, was synthesized by a similar method as compound
- 15 **213e** to afford a foam (88%):  $[\alpha]_D^{24} +74.2^\circ$  (c 0.36, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3332, 3235, 1793, 1664, 1537, 1448, 1416, 1337, 1169, 118, 1092, 940, 690; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.99 (1H, s), 7.88 (2H, d, J = 6.8), 7.64-7.48 (3H, m), 7.34 (5H, s), 7.13 (1H, d, J = 6.9), 5.39 (1H, s), 4.81
- 20 (2H, m), 4.62 (1H, d, J = 11.5), 4.48 (1H, m), 4.33 (1H, m), 3.85 (1H, m), 3.59 (2H, m), 3.03 (1H, dd, J = 7.6, 18.2), 2.49-2.28 (3H, m), 1.94-1.40 (4H, m). Anal. Calcd for C<sub>26</sub>H<sub>29</sub>SN<sub>5</sub>O<sub>8</sub>: C, 54.63; H, 5.11; N, 12.25. Found: C, 54.42; H, 5.28; N, 11.62. MS (ES<sup>+</sup>) 572 (MH<sup>+</sup>, 100%). Accurate mass calculated for C<sub>26</sub>H<sub>30</sub>SN<sub>5</sub>O<sub>8</sub> (MH<sup>+</sup>): 572.1815. Found: 572.1802.

- [4S(2RS,3S)] 7-(4-Benzylloxyphenyl)carbonylamino-N-(2-benzylloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide**
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(264k), was prepared by the method used for 213e (96%):  
IR (KBr) 3294, 2946, 1793, 1658, 1606, 1535, 1501,  
1248, 1174, 1119. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.91 (1H, s), 7.85  
(3H, m), 7.4 (10H, m), 7.02 (2H, d), 5.35 (1H, s), 5.10  
5 (2H, s), 4.8-4.3 (5H, m), 4.00 (1H, bs), 3.78 (2H, m),  
2.90 (2H, m), 2.5-1.5 (6H, m).

[4S(2RS,3S)] N-(2-Benzoyloxy-5-oxotetrahydrofuran-3-yl)-  
6,10-dioxo-7-(3,4-methylenedioxycarbonylamino)-  
1,2,3,4,7,8,9,10-octahydro-6H-

10 pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide  
(264l), was prepared by a similar method as compound  
213a to afford a mixture of diastereomers (syn:anti  
isomer ratio 1:1) as a white solid (1.72g, 71%): mp.  
148-60°C; IR (KBr) 3314, 1780, 1677, 1658, 1651, 1550,  
15 1485, 1439, 1258, 1132, 1038, 943; <sup>1</sup>H NMR (D<sub>6</sub>-DMSO) δ  
10.39 (1H, s), 8.71 (0.5H, d), 8.49 (0.5H, d), 7.44  
(1H, d), 7.42-7.30 (6H, m), 7.03 (1H, d), 6.12 (2H, s),  
5.68 (0.5H, d), 5.45 (0.5H, s), 4.90-4.82 (1H, m),  
4.82-4.58 (2.5H, m), 4.40-4.10 (1.5H, m), 3.90-3.65  
20 (2H, m), 3.65-3.43 (1H, m), 3.09 (0.5H, dd), 2.90-2.55  
(1.5H, m), 2.45-2.10 (2H, m), 2.10-1.35 (4H, m). Anal.  
Calcd for C<sub>28</sub>H<sub>29</sub>N<sub>5</sub>O<sub>9</sub>·0.2H<sub>2</sub>O: C, 57.67; H, 5.08; N,  
12.01. Found: C, 58.01; H, 5.33; N, 11.51. MS (ES<sup>+</sup>)  
581 (M<sup>+</sup> + 2, 33%), 580 (M<sup>+</sup>, 100), 374 (9), 373 (48),  
25 345 (12), 261 (4), 239 (7), 149 (9).

[3S(4S)] 3-[6,10-Dioxo-7-(2-naphthalenesulfonyl)amino-  
1,2,3,4,7,8,9,10-octahydro-6H-  
pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-  
oxobutanoic acid (265a), was prepared by a similar  
30 method as compound 265 to afford a white solid (37mg,



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17%): mp. 126-30°C (dec);  $[\alpha]_D^{20} +30^\circ$  (c 0.05, MeOH);  
 IR (KBr) 3371, 2935, 1785, 1663, 1538, 1418, 1339,  
 1164, 669;  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  8.44 (1H, s), 8.06-7.50 (7H,  
 m), 7.22 (1H, d,  $J = 8.4$ ), 4.58-4.57 (1H, m), 4.46-4.42  
 5 (1H, m), 4.16-4.09 (2H, m), 3.85-3.50 (3H, m), 2.84-  
 2.78 (1H, m), 2.64-2.51 (1H, m), 2.44-2.15 (2H, m),  
 1.81-0.89 (4H, m). Anal. Calcd for  $\text{C}_{23}\text{H}_{25}\text{N}_5\text{O}_8\text{S}\cdot\text{H}_2\text{O}$ : C,  
 50.27; H, 4.95; N, 12.74. Found: C, 50.33; H, 5.04; N,  
 12.60. MS ( $\text{ES}^+$ ) 530.

10 [3S(4S)] 3-[6,10-Dioxo-7-(3-methoxyphenylureido)-  
 1,2,3,4,7,8,9,10-octahydro-6H-  
 pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-  
 oxobutanoic acid (265c), was prepared by a similar  
 method as 265, (90%) as a colourless solid: mp.  $\sim 150^\circ\text{C}$   
 15 (decomp.);  $[\alpha]_D^{23} +94.8^\circ$  (c 0.1, 20% MeOH/ $\text{CH}_2\text{Cl}_2$ ); IR  
 (KBr) 3330, 1780, 1660, 1610, 1550, 1495, 1428, 1326,  
 1287, 1251, 1223, 1160;  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.16 (2H, m),  
 6.89 (1H, d,  $J = 7.8$ ), 4.58 (1H, m), 4.37 (2H, m), 3.76  
 (6H, s + m), 2.95 (1H, m), 2.67 (1H, m), 2.33 (1H, m),  
 20 2.20-1.85 (3H, m), 1.66 (1H, m).

[3S(4S)] 3-[6,10-Dioxo-7-(2-methoxyphenylureido)-  
 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]-  
 triazepine-4-carboxamido]-4-oxobutanoic acid (265d),  
 was prepared by a similar method as 265, (85%) as a  
 25 colourless solid: mp.  $\sim 176-85^\circ\text{C}$ ;  $[\alpha]_D^{23} +11.0^\circ$  (c 0.1,  
 MeOH); IR (KBr) 3392, 3328, 1784w, 1665, 1603, 1537,  
 1490, 1462, 1437, 1337, 1290, 1290, 1217, 1177, 1119,  
 1023;  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  8.02 (2H, m), 6.95 (4H, m), 5.05  
 (1H, m), 4.60 (2H, m), 3.92 (4H, s + m), 3.00 (2H, m),  
 30 2.68 (1H, m), 2.39 (1H, m), 2.00 (4H, m), 1.69 (1H, m).

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- [3S(4S)] 3-(6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylacetylamino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido)-4-oxobutanoic acid (1095), was prepared by a similar method as compound 265 to afford a white solid (84mg, 90%): mp. 180-6°C;  $[\alpha]_D^{22} +22.3^\circ$  (c 0.065, CH<sub>3</sub>OH); IR (KBr) 3700-2300 (br), 3287, 1664, 1536, 1425, 1261, 1181; <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  7.35-7.20 (5H, m), 5.00-4.90 (1H, m), 4.60-4.50 (1H, m), 4.50-4.10 (2H, m), 3.90-3.50 (3H, m), 3.54 (2H, s), 3.00-2.80 (1H, m), 2.80-2.40 (2H, m), 2.35-2.20 (1H, m), 2.20-1.50 (4H, m). MS (ES<sup>+</sup>) 459 (M<sup>+</sup> 24%), 458 (M<sup>+</sup> - 1, 100), 358 (27), 175 (9), 149 (7), 137 (12). Accurate mass calculated for C<sub>21</sub>H<sub>26</sub>N<sub>5</sub>O<sub>7</sub> (MH<sup>+</sup>): 460.1832. found: 460.1840.
- 15 [3S(4S)] 3-[6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-7-(3-phenylureido)-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-oxobutanoic acid (265f), was prepared by a similar method as compound 265 to afford a white foamy solid (130mg, 88%): mp. 157-62°C;  $[\alpha]_D^{24} +41.7^\circ$  (c 0.1, CH<sub>3</sub>OH); IR (KBr) 3700-2300 (br), 3325, 1782, 1663, 1547, 1443, 1315, 1242, 1181; <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  7.40 (2H, dd), 7.35-7.20 (2H, m), 7.06-6.95 (1H, m), 5.05-4.95 (1H, m), 4.64-4.54 (1H, m), 4.50-4.35 (1H, m), 4.35-4.15 (1H, m), 3.90-3.69 (3H, m), 3.00-2.85 (1H, m), 2.80-2.45 (3H, m), 3.40-1.50 (4H, m). MS (ES<sup>+</sup>) 460 (M<sup>+</sup>, 24%), 459 (M<sup>+</sup> - 1, 100), 341 (9), 340 (54), 296 (6), 239 (9).
- [3S(4S)] 3-[6,10-Dioxo-7-(indole-2-carboxamido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-
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oxobutanoic acid (1075), was prepared by a similar method as compound 265 to afford a white solid (184mg, 83%): mp. 210-5°C;  $[\alpha]_D^{24} +43.9^\circ$  (c 0.1, CH<sub>3</sub>OH); IR (KBr) 3700-2300 (br), 3309, 1660, 1537, 1423, 1311, 1262, 1184; <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  7.61 (1H, d), 7.45 (1H, d), 7.28-7.15 (1H, m), 7.15-7.00 (1H, m), 7.13 (1H, s), 5.12-4.96 (1H, m), 4.62-4.55 (1H, m), 4.50-4.25 (2H, m), 4.00-3.69 (3H, m), 3.05-2.90 (1H, m), 2.80-2.30 (3H, m), 2.25-1.50 (4H, m). MS (ES<sup>+</sup>) 484 (M<sup>+</sup>, 26%), 483 (M<sup>+</sup> - 1, 100), 383 (25), 245 (12), 208 (11), 200 (21), 174 (31), 137 (18).

[3S(4S)] 3-{7-[(4-Acetamido)benzamido]-6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]-triazepine-4-carboxamido}-4-oxobutanoic acid (1018), was prepared by a similar method as compound 265 to afford a white solid (177mg, 82%): mp. 235-40°C;  $[\alpha]_D^{23} +27.3^\circ$  (c 0.1, CH<sub>3</sub>OH); IR (KBr) 3700-2300 (br), 3311, 2957, 1662, 1599, 1531, 1318, 1266, 1182; <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  7.83 (2H, d), 7.69 (2H, d), 5.10-4.95 (1H, m), 4.64-4.55 (1H, m), 4.50-4.35 (1H, m), 4.32-4.22 (1H, m), 4.00-3.65 (3H, m), 3.05-2.90 (1H, m), 2.80-2.30 (3H, m), 2.15 (3H, s), 2.15-1.50 (4H, m). Anal. Calcd for C<sub>22</sub>H<sub>26</sub>N<sub>6</sub>O<sub>8</sub>•1.5H<sub>2</sub>O: C, 49.90; H, 5.52; N, 15.87. Found: C, 50.21; H, 5.41; N, 15.49. MS (ES<sup>+</sup>) 502 (M<sup>+</sup>, 28%), 501 (M<sup>+</sup> - 1, 100), 401 (8), 218 (4), 119 (2), 116 (5), 113 (16).

[3S(4S)] 3-[6,10-Dioxo-7-(4-methoxybenzoylamino)-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-oxobutanoic acid (1052), was synthesized via method used to prepare 265 to afford a white solid

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(0.194g, 100%): mp. 138-142°C;  $[\alpha]_D^{20} +36.3^\circ$  (c 0.19, CH<sub>3</sub>OH); IR (KBr) 3434-2962, 1782, 1660, 1607, 1537, 1504, 1441, 1424, 1313, 1293, 1258, 1177; <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  7.11 (2H, d, J = 8.8), 6.90 (2H, d, J = 8.9),  
5 4.48 (1H, m), 4.34, 4.28 (1H, 2m), 4.15 (1H, m), 3.75 (3H, s), 3.75, 3.70 (3H, m), 2.88, 2.49, 2.28, 2.23, 2.00, 1.86, 1.79, 1.58 (8H, m).

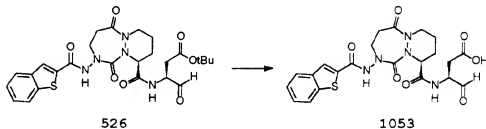
[3S(4S)] 3-(6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylsulphonylamino-6H-  
10 pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido)-4-oxobutanoic acid (1027), was synthesized by a similar method as compound 265 to afford a white foam (88%):  
 $[\alpha]_D^{24} +22.6^\circ$  (c 0.17, MeOH); IR (KBr) 3349, 1789, 1663, 1537, 1448, 1337, 1169, 1092, 690; <sup>1</sup>H NMR (CD<sub>3</sub>OD)  
15  $\delta$  7.82 (2H, d, J = 7.8), 7.57 (3H, m), 4.74 (1H, m), 4.47 (1H, m), 4.24-4.10 (2H, m), 3.72-3.47 (4H, m), 2.62-2.48 (3H, m), 2.20 (1H, m), 1.94-1.35 (3H, m). MS (ES<sup>+</sup>) 480 (M<sup>+</sup> - 1, 100%). Accurate mass calculated for C<sub>19</sub>H<sub>24</sub>SN<sub>5</sub>O<sub>8</sub> (MH<sup>+</sup>): 482.1346. Found: 482.1325.

20 [3S(4S)] 3-[6,10-Dioxo-7-(4-hydroxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-oxobutanoic acid (1056), was prepared by the method used for 265 (95%): mp. >300°C; IR (KBr) 3392, 1660,  
25 1610, 1507, 1442, 1280, 1171, 1149, 1133. <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  7.74 (2H, d J = 8.7), 6.84 (2H, d J = 8.7) 4.56 (1H, m), 4.41 (1H, bd, J = 12.6), 4.28 (1H, m), 3.85 (3H, m), 2.98 (1H, m), 2.8-2.3 (3H, m), 2.3-1.6 (4H, m).

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[3S(4S)] 3-[6,10-Dioxo-7-(3,4-methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-oxobutanoic acid (1015), was prepared by a similar

5 method as used for 265 to afford a white solid (142mg, 58%): mp. 170-5°C;  $[\alpha]_D^{25} +32.7^\circ$  (c 0.1, CH<sub>3</sub>OH); IR (KBr) 3700-2500 (br), 3325, 2969, 1784, 1662, 1485, 1440, 1292, 1258, 1037; <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  7.45 (1H, dd), 7.32 (1H, d), 6.90 (1H, d), 6.05 (2H, s), 5.10-4.90  
10 (1H, m), 4.62-4.54 (1H, m), 4.45-4.35 (1H, m), 4.33-4.22 (1H, m), 3.95-3.65 (3H, m), 3.05-2.90 (1H, m), 2.80-2.30 (3H, m), 2.20-1.50 (4H, m).



[3S(4S)] t-Butyl 3-[7-(benzo[b]thiophene-2-carbonyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine]-4-oxobutanoate semicarbazone (526), was prepared by a similar method

15 as used for 502 to afford a glassy solid:  $[\alpha]_D^{20} +34^\circ$  (c 0.13, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3437, 2929, 1670, 1530, 1428, 1288, 1156; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  10.0 (1H, bs), 9.74 (1H, bs), 7.93 (1H, s), 7.80-7.60 (2H, m), 7.40-7.18 (3H, m), 6.15-5.30 (2H, bs), 5.00-4.85 (2H, m), 4.50-4.25 (1H, m), 3.95-3.75 (3H, m), 3.12-2.78 (2H, m),  
20 2.73-1.60 (7H, m), 1.36 (9H, s). Anal. Calcd for

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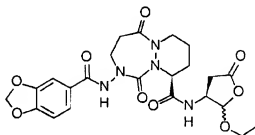
$C_{27}H_{34}N_8O_7S$ : C, 52.76; H, 5.58; N, 18.23. Found: C, 52.25; H, 5.74; N, 16.30. MS ( $ES^+$ ) 615.

[3S(4S)] 3-[7-(Benzo[b]thiophene-2-carbonyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-

5 pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-oxobutanoic acid (1053), was prepared by a similar

method as used for 214 to afford a white solid (106mg, 73%):  $[\alpha]_D^{20} +22^\circ$  (c 0.10, MeOH); IR (KBr) 3428, 2944, 1733, 1652, 1532, 1433, 1337, 1288, 1186;  $^1H$  NMR

10  $(CD_3OD)$   $\delta$  7.95 (1H, s), 7.90-7.85 (2H, m), 7.43-7.35 (2H, m), 4.98 (1H, m), 4.65-4.52 (1H, m), 4.40-4.20 (2H, m), 3.85-3.70 (3H, m), 3.30-3.25 (3H, m), 3.03-2.85 (1H, m), 2.70-2.31 (3H, m), 2.10-1.55 (4H, m). MS ( $ES^+$ ) 500 (as methyl acetal of the aldehyde).



15

528

[4S(2RS,3S)] 6,10-Dioxo-N-(2-ethoxy-5-

oxotetrahydrofuran-3-yl)-7-(3,4-

methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide

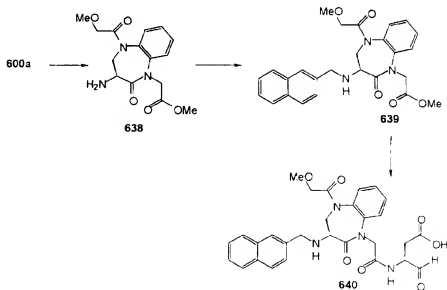
20 (528), was prepared by a similar method as compound 213e to afford a mixture of diastereomers (Syn: anti isomer ratio 1:1) as a creamy white foamy solid (1.05g,

- 681 -

58%): mp. 124-32°C; IR (KBr): 3312, 2979, 1790, 1664, 1610, 1532, 1485, 1285, 1120, 1037, 932; <sup>1</sup>H NMR (D<sub>6</sub>-DMSO) δ 10.39 (1H, s), 8.71 (0.5H, d), 8.43 (0.5H, d), 7.45 (1H, d), 7.36 (1H, s), 7.04 (1H, d), 6.12 (2H, s), 5.58 (0.5H, d), 5.34 (0.5H, s), 4.95-4.85 (1H, m), 4.70-4.52 (0.5H, m), 4.35-4.10 (1.5H, m), 3.95-3.50 (5H, m), 3.03 (0.5H, dd), 2.90-2.55 (1.5H, m), 2.46-2.20 (2H, m), 2.10-2.40 (4H, m), 1.16-1.13 (3H, 2 x t). Anal. Calcd for C<sub>23</sub>H<sub>27</sub>N<sub>5</sub>O<sub>9</sub>·0.6H<sub>2</sub>O: C, 52.29; H, 5.38; N, 13.26. Found: C, 52.53; H, 5.35; N, 12.78. MS (ES<sup>+</sup>) 519 (M<sup>+</sup> + 2, 27%), 518 (M<sup>+</sup> + 1, 100), 472 (7), 374 (12), 373 (53), 345 (14), 149 (12).

Example 31

Compounds 640, 642, 645, 650, 653, 655, 656, 662, 668, 669, 670, 671, 677, 678, 681, 682, 683, 684, 686, 688a, 688b, 689i, 689b, 690a, 690b, 691a, 691b, 695a, 695b, 695c, 692a, 692b, 693 and 694 were prepared as follows.



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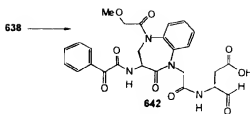
(3S)-2-Oxo-3-amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester (638), was synthesized from 600a by methods similar to those used for making 602m from 600a to afford 2.4g of 638 as a white solid.

(3S)-2-Oxo-3-(2-naphthylmethylene)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester (639). To a solution of 638 (630 mg, 1.76 mmol) and 2-naphthylmethyl bromide (428 mg, 1.94 mmol) in CH<sub>3</sub>CN was added K<sub>2</sub>CO<sub>3</sub> (608 mg, 4.4 mmol). The resulting mixture was stirred at ambient temperature. After 18 hours, the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed with water then brine, dried over Na<sub>2</sub>SO<sub>4</sub> then concentrated in vacuo. Flash chromatography (SiO<sub>2</sub>, 0 to 20% EtOAc/CH<sub>2</sub>Cl<sub>2</sub>) afforded 450mg of 639.

(3S)-3-[(3S)-2-Oxo-3-(2-naphthylmethylene)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetyl-amino]4-oxo-butyric acid (640), was synthesized by methods used to make 605v from 602v to afford 205 mg of 640 as a white solid, <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.4-2.55(m, 1H), 2.65-2.8(m, 1H), 3.2(s, 3H), 3.72-3.78(m, 1H), 3.85-4.0(m, 2H), 4.22-4.28(d, 1H), 4.26-4.5(m, 4H), 4.58-4.75(m, 1H), 4.78-4.85(m, 1H), 5.0-5.08(t, 1H), 7.35-7.65(m, 7H), 7.85-8.02(m, 4H).

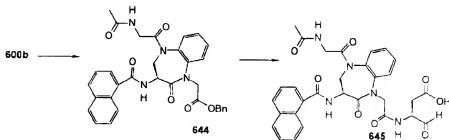
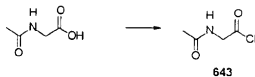


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(3S)-3-[(3S)-2-Oxo-3-benzoylformylamino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetyl-amino]4-oxo-butyrac acid (642), was synthesized from 638 by similar methods used to make 605m to afford

5 213 mg of 642,  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  2.5(m, 1H), 2.68(ddd, 1H), 3.25(s, 2H), 3.3(s, 3H), 3.78(m, 2H), 4.0(d, 1H), 4.3(m, 1H), 4.6(m, 2H), 4.85(br. s, 2H), 7.08-7.22(m, 2H), 7.35(m, 1H), 7.4-7.65(m, 4H), 7.7(dd, 1H), 8.1(cd, 1H).



10 2-Acetamido-acetyl chloride (643). To a suspension of N-acetyl glycine (200 mg, 1.7 mmol) in  $\text{CH}_2\text{Cl}_2$  (2.5 mLs) containing DMF (0.005 mLs) was added oxalyl chloride

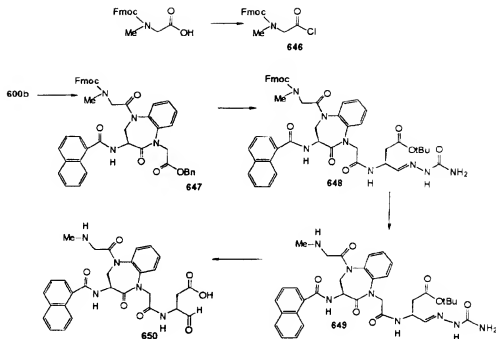
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(0.450 mLs, 5.1 mmol). After stirring 30 minutes at ambient temperature, the mixture was concentrated to afford **643** as a crude product.

(3S)-2-Oxo-3-(1-naphthoyl)amino-5-(2-acetamido)acetyl-  
5 2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid  
benzyl ester (**644**), was synthesized from **600b** by  
methods used to make **602d** from **600b** using **643** to afford  
112 mg of **644**.

(3S)-3-[(3S)-2-Oxo-3-(1-naphthoyl)amino-5-(2-  
10 acetamido)acetyl-2,3,4,5-tetrahydro-1H-1,5-  
benzodiazepine-1-acetylamino]4-oxo-butyric acid (**645**),  
was synthesized from **644** by methods used to make **605d**  
from **602d** to afford 43 mg of **645** as a white solid, <sup>1</sup>H  
NMR (CD<sub>3</sub>OD) δ 1.95(s, 3H), 2.4(m, 1H), 2.65(m, 1H),  
15 3.4(s, 1H), 3.55(m, 1H), 3.85(m, 1H), 4.05(d, 1H),  
4.3(m, 1H), 4.4-4.6(m, 2H), 5.0(m, 1H), 7.4-7.7(m, 6H),  
7.85-8.0(m, 2H).

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2-(*N*-Methyl, *N*-fluorenylmethoxycarbonyl)aminoacetyl chloride (646), was prepared from *N*-Fmoc-sarcosine by method used to make 643 to afford 646 as a crude product.

- 5 (3*S*)-2-Oxo-3-(1-naphthoyl)amino-5-[2-(*N*-methyl, *N*-fluorenylmethoxycarbonyl)amino]acetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetic acid benzyl ester (647), was synthesized from 600b by methods used to synthesize 602d from 600b, using 646 to afford 481
- 10 mg of 647.

(3*S*)-3-[(3*S*)-2-Oxo-3-(1-naphthoyl)amino-5-[2-(*N*-methyl, *N*-fluorenylmethoxycarbonyl)amino]acetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid *tert*-butyl ester semicarbazone (648), was

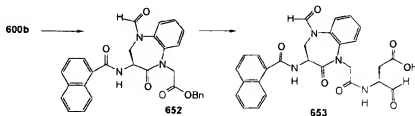
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synthesized from **647** by methods used to prepare **604d** from **602d** to afford 409 mg of **648**.

(3*S*)-3-[(3*S*)-2-Oxo-3-(1-naphthoyl)amino-5-(2-methylamino) acetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetyl-amino]4-oxo-butyric acid *tert*-butyl ester semicarbazone (**649**).

A solution of **648** (409 mg, 0.465 mmol) in MeCN:Et<sub>2</sub>NH (4:1, v/v) was stirred at ambient temperature. After 45 minutes, the reaction mixture was concentrated in vacuo. Flash chromatography (SiO<sub>2</sub>, 5% to 20% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) afforded 241 mg of **649**.

(3*S*)-3-[(3*S*)-2-Oxo-3-(1-naphthoyl)amino-5-(2-methylamino) acetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetyl-amino]4-oxo-butyric acid (**650**), was synthesized from **649** by methods used to prepare **605d** from **604** to afford 179 mg of **650** as a white solid, <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 2.4-2.6(m, 2H), 2.7(s, 3H), 3.5(q, 1H), 3.8(m, 2H), 4.2-4.4(m, 2H), 4.3-4.45(m, 1H), 5.0-5.1(m, 2H), 7.4-7.7(m, 6H), 7.85-7.9(m, 2H), 8.2(m, 1H).

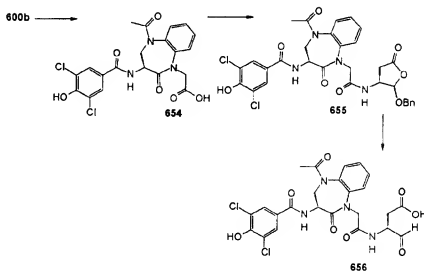


(3*S*)-2-Oxo-3-(1-naphthoyl)amino-5-formyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetic acid benzyl ester (**652**), was synthesized from **600b** by methods similar to those used to make **602n** from **600b**, using the

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reagent obtained from reacting DMF with 3 equiv. of oxalyl chloride in a  $\text{CH}_2\text{Cl}_2$  solution as  $\text{R}^3\text{X}$ , to afford 404 mg of **652**.

- (3S)-3-[(3S)-2-Oxo-3-(1-naphthoyl)amino-5-formyl-  
 5 2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetyl-  
 amino]4-oxo-butyric acid (**653**), was synthesized  
 from **652** by methods used to prepare **605d** from **602d** to  
 afford 84 mg of **653** as a white solid,  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$   
 2.3(m, 1H), 2.55(dd, 1H), 3.75(br. s, 1H), 4.25-4.6(m  
 10 5H), 5.15(m, 1H), 7.2-7.45(m, 6H), 7.8-7.9(dd, 3H),  
 8.1(s, 1H), 8.2(m, 2H).



- (3S)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-  
 acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-  
 acetic acid (**654**), was synthesized from **600b** using  
 15 methods similar to those used for preparing **603d** from  
**600b** to afford 775 mg of **654**.

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(3*S*)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-acetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetamide (**655**), was synthesized from **654** using the  
5 method used to prepare **213e** to afford 304 mg of **655**, <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 2.4(d, 1H), 2.6-2.75(m, 2H), 3.0(m, 1H), 3.45(m, 1H), 3.8(d, 1H), 4.0(t, 2H), 4.4(m, 2H), 4.5-4.55(m, 2H), 7.2-7.45(m, 4H), 7.85(s, 2H).

(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dichloro, 4-hydroxybenzoyl)amino-5-acetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetylamino]4-oxo-butyrlic acid (**656**), was synthesized from **655** using a method similar to that used to prepare **2002** from **2001** to afford 136 mg of **656** as a white solid, <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 1.85(s, 3H),  
10 2.5(m, 1H), 2.65(m, 1H), 3.7(m, 1H), 4.3(m, 1H),  
15 4.55(m, 2H), 7.4-7.6(m, 4H), 7.85(s, 2H).



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2-(Fluorenylmethoxycarbonyl)hydroxyacetic acid benzyl ester (657). To a solution of benzyl glycolate (6.0 g, 36.1 mmol) in  $\text{CH}_2\text{Cl}_2$ , cooled via ice-water bath, was added fluorenylmethoxy chloroformate (14 g, 1.5 equiv.) then diisopropylethylamine (9 mLs, 1.5 equiv.). After 1 hour, reaction mixture was poured into a saturated aqueous solution of ammonium chloride and extracted with  $\text{CH}_2\text{Cl}_2$ , dried over  $\text{Na}_2\text{SO}_4$  then concentrated in vacuo. The product was triturated from MeOH to obtain 2.2 g of 657 as a first crop of white solid.

2-(Fluorenylmethoxycarbonate) acetic acid (658). To a solution of 657 (2.2 g, 5.93 mmol) in tetrahydrofuran was added 5% Pd/C (220 mg). The resulting suspension was vigorously stirred under hydrogen atmosphere. After 90 min, the reaction mixture was filtered through Celite. The filtrate was poured into saturated aqueous  $\text{NaHCO}_3$  and washed twice with EtOAc. The aqueous layer was then acidified and the product extracted twice with  $\text{CH}_2\text{Cl}_2$ , dried over  $\text{Na}_2\text{SO}_4$  and concentrated in vacuo to afford 1.46 g (88%) of 658 as a white solid.

2-(Fluorenylmethoxycarbonate) acetyl chloride (659), was prepared from 658 by the method used to prepare 643 to afford 659 as a crude product.

(3S)-3-[(3S)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-(2-fluorenylmethoxycarbonate)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid tert-butyl ester semicarbazone (660), was synthesized



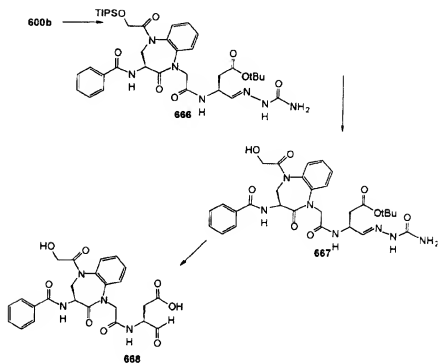
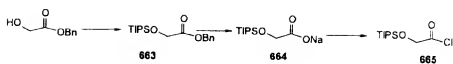
- 691 -

from 600b, using 659, by methods used to prepare 604d from 600b to afford 453 mg of 660.

(3S)-3-[(3S)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-(2-hydroxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyr  
5 ic acid tert-butyl ester semicarbazone (661). A solution of 660 (423 mg) in MeOH:Et<sub>2</sub>NH (1:1, v/v) was stirred at ambient temperature. After 10 minutes, the reaction mixture was concentrated *in vacuo* to a small  
10 volume. Precipitation by the addition of ether afforded 230 mg of 661.

(3S)-3-[(3S)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-(2-hydroxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-  
15 butyric acid (662), was synthesized from 661 by the methods used to prepare 605d from 604 to afford 37 mg of 662 as a white solid, <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 2.45(m, 1H), 2.7(m, 1H), 3.75(m, 1H), 3.9(d, 1H), 4.15(d, 1H), 4.35(m, 1H), 4.5(t, 2H), 4.7(dd, 1H), 7.4-7.6(m, 4H),  
20 7.85(s, 2H).

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**2-(Triisopropylsilyloxy)acetic acid benzyl ester (663).**

To a solution of benzyl glycolate (46.91g, 0.282 mol) and diisopropylethylamine (74 mLs, 0.423 mol) in  $\text{CH}_2\text{Cl}_2$ , cooled via water bath, was added a solution of  
5 TIPSOTf (95 g, 0.31 mol) in  $\text{CH}_2\text{Cl}_2$ . The resulting mixture was allowed to warm to ambient temperature then poured into water, washed twice with 10% aqueous  $\text{NaHSO}_4$ , dried over  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo*. Flash chromatography ( $\text{SiO}_2$ , 0 to 5% EtOAc in hexanes)  
10 afforded 71.6 g of **663**.

**2-(Triisopropylsilyloxy)acetic acid (664).**

To a solution of **663** (0.4 g, 1.2 mmol) in EtOAc was added 10% Pd/C (33 mg). The resulting suspension was stirred under hydrogen atmosphere. After 15 hours, the  
15 reaction mixture was filtered through Celite and the filtrate concentrated *in vacuo* to afford 0.29 g of an oil. To a solution of this oil in 1,4-dioxane was added  $\text{NaHCO}_3$  (0.5M, 2.4 mLs). The resulting solution was concentrated *in vacuo* from toluene to afford **664** as  
20 a waxy solid.

**2-(Triisopropylsilyloxy)acetyl chloride (665)**, was synthesized from **664** by a method similar that used to prepare **643** to afford **665** as a crude product.

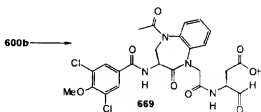
**(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-(2-**

25 triisopropylsilyloxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyrlic acid tert-butyl ester semicarbazone (**666**), was synthesized from **600b**, using **665**, by methods used to prepare **604d** from **600b** to afford 131 mg of **666**.

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(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-(2-hydroxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid *tert*-butyl ester semicarbazone (**667**). To a solution of **666** (131 mg, 0.17 mmol) in tetrahydrofuran, cooled via ice-water bath, was added tetrabutylammonium fluoride (1M, 0.190 mL). After 2 hours the reaction mixture was poured into water, extracted twice with EtOAc, dried over MgSO<sub>4</sub> and concentrated *in vacuo* to afford 63 mg of **667** as a white solid.

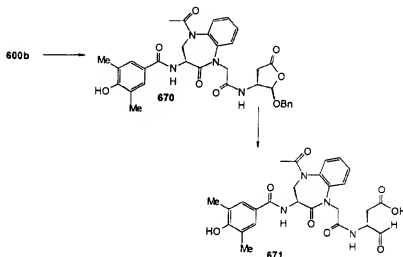
(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-(2-hydroxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (**668**), was synthesized from **667** by the methods used to prepare **605d** from **604d** to afford 48 mg of **668** as a white solid, <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 2.45(m, 1H), 2.67(dddd, 1H), 3.78(d, 1H), 3.85(br. m, 1H), 4.05(d, 1H), 4.28(m, 1H), 4.5(m, 2H), 4.65(m, 1H), 4.95(br. s, 2H), 7.4-7.5(m, 4H), 7.52-7.65(m, 3H), 7.88(d, 2H).



(3S)-3-[(3S)-2-Oxo-3-(3,5-dichloro-4-methoxybenzoyl)amino-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (**669**), was synthesized from **600b** by the methods used to prepare **605d** from **600b** to afford 63 mg of **669** as a

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white solid,  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  1.9(s, 3H), 2.4-2.7(m, 2H), 3.6-3.7(m, 2H), 3.9(s, 3H), 4.2-4.4(m, 2H), 4.4-4.6(m, 3H), 7.4-7.8(m, 4H), 7.9(s, 2H).

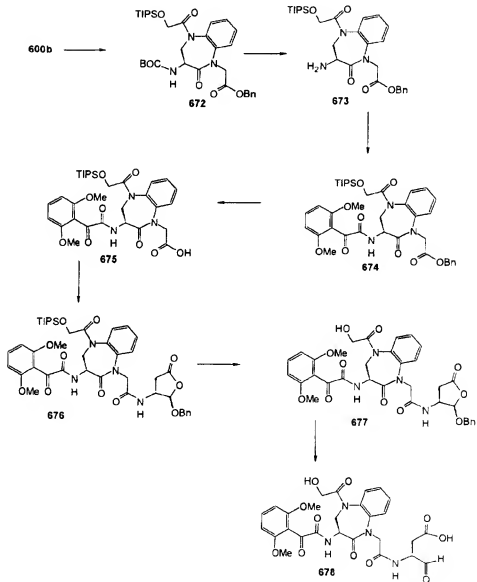


(3S)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-acetyl-N-[(2RS,3S)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (670), was synthesized from 600b by the methods used to prepare 655 from 600b to afford 218 mg of 670 as a white solid,  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  1.7, 1.75(2s, 3H), 2.15, 2.2(2s, 6H), 2.4-2.5(m, 1H), 2.6-2.75(m, 1H), 3.65-3.75(m, 2H), 4.2-4.3(m, 2H), 4.45-4.6(m, 3H), 7.35-7.6(m, 4H), 7.5(s, 2H).

(3S)-3-[(3S)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetyl]amino-4-oxo-butanoic acid (671), was synthesized from 670 by the methods used to prepare 2002 from 2001 to afford 253 mg of 671 as a white solid,  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  1.9(s, 3H), 2.25(s, 6H),

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2.4-2.5 (m, 1H), 2.6-2.75 (m, 1H), 3.65-3.75 (m, 2H), 4.2-4.3 (m, 2H), 4.45-4.6 (m, 3H), 7.35-7.6 (m, 4H), 7.5 (s, 2H).



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(3S)-2-Oxo-3-*tert*-butoxycarbonylamino-5-(2-triisopropylsilyloxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzylester (672), was synthesized from 600b by method 1 used to prepare 602n from 600b using 665 to afford 1.08 g of 672.

(3S)-2-Oxo-3-amino-5-(2-triisopropylsilyloxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzylester (673). To a solution of 672 (1.08 g, 1.69 mmol) in CH<sub>2</sub>Cl<sub>2</sub> was added 2,6-lutidine (0.8 mL) then TMSOTf (1 mL, 5.1 mmol). After 1 hour, the reaction mixture was poured into NaHCO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried over MgSO<sub>4</sub> and concentrated *in vacuo* to a small volume that was used directly for the next reaction.

(3S)-2-Oxo-3-(1,6-dimethoxybenzoyl formyl)amino-5-(2-triisopropylsilyloxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzylester (674), was synthesized from 673 by the method used to prepare 602b to afford 0.91 g of 674.

(3S)-2-Oxo-3-(1,6-dimethoxybenzoyl formyl)amino-5-(2-triisopropylsilyloxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid (675). A solution of 674 (0.365 g, 0.5 mmol) in MeOH was stirred with 1N NaOH (1.2 mL, 1.2 mmol). After 16 hours the reaction mixture was concentrated *in vacuo* then dissolved in water and washed twice with ether. The aqueous layer was acidified with 1N HCl and the product extracted with EtOAc, dried over MgSO<sub>4</sub> and concentrated *in vacuo* to afford 337 mg of 675 as a solid.

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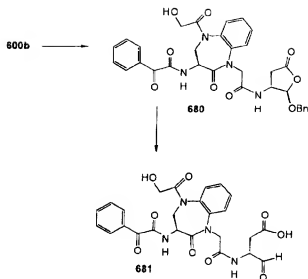
(3*S*)-2-Oxo-3-(1,6-dimethoxybenzoylformyl)amino-5-(2-triisopropylsilyloxy)acetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetamide (**676**), was synthesized from **675** by the method used to prepare **213e** to afford 166 mg of **676** as a white solid.

(3*S*)-2-Oxo-3-(1,6-dimethoxybenzoylformyl)amino-5-(2-hydroxy)acetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetamide (**677**). A solution of TBAF (6 mL, 3 mmol) in HOAc (0.46 mL, 8 mmol) was added to **676** (0.213 g, 0.256 mmol). After 16 hours the reaction mixture was poured into EtOAc and washed twice with NaHCO<sub>3</sub>, once with brine then dried over MgSO<sub>4</sub> and concentrated in *vacuo* to afford 139 mg of **677** as a solid, <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.4(d, 1H), 2.5(dd, 1H), 2.6(dd, 1H), 2.92(dd, 1H), 3.15(m, 2H), 3.55-3.65(m, 2H), 3.72(s, 6H), 3.92(m, 1H), 4.05(m, 1H), 4.3(m, 1H), 4.42(d, 1H), 4.6(dd, 1H), 4.65-4.8(m, 2H), 4.88(d, 1H), 5.55(d, 1H), 6.55(m, 2H), 6.75(d, 1H), 7.25-7.55(m, 8H), 7.75(m, 2H).

(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dimethoxybenzoylformyl)amino-5-(2-hydroxy)acetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetyl-amino]4-oxo-butyrac acid (**678**), was synthesized by the method used to prepare **667** from **666** to afford 54 mg of **678** as a white solid, <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 2.45(m, 1H), 2.7(m, 1H), 3.5(m, 2H), 3.75(br. s, 6H), 4.05(d, 1H), 4.3(m, 1H), 4.51-4.6(m, 2H), 4.8(br. m, 2H), 6.7(d, 2H), 7.4-7.5(br. m, 3H), 7.6-7.65(br. m, 2H).



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(3*S*)-2-Oxo-3-benzoylformylamino-5-(2-hydroxy)acetyl-N-(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetamide (**680**), was synthesized from **600b** by the methods used to prepare

5 **677** from **600b** to afford 140 mg of **680** as a white solid, <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.31(d, 1H), 2.4(dd, 2H), 2.75(dd, 2H), 2.85(dd, 1H), 3.36(br. s, 1H), 3.45(br. s, 1H), 3.6(br. t, 2H), 3.82(br. m, 2H), 3.95(br. d, 2H), 4.35(m, 2H), 4.42(d, 1H), 4.55(m, 1H), 4.70(d, 1H), 4.82(br. s, 2H),

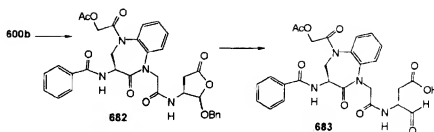
10 5.5(d, 1H), 6.91(d, 1H), 7.25(br. m, 5H), 7.35-7.46(br. m, 3H), 7.5-7.6(m, 2H), 8.15(br. d, 2H).

(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylformylamino-5-(2-hydroxy)acetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetylamino]4-oxo-butyrac acid (**681**), was synthesized from **680** by the method used to prepare

15 **678** from **677** to afford 45 mg of **681** as a grey solid, <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 2.5(m, 1H), 2.7(dt, 1H), 3.65-3.85(br. m, 3H), 4.05(m, 1H), 4.3(m, 1H), 4.5-4.7(br. m, 3H),

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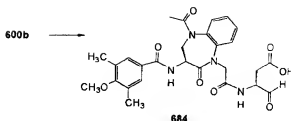
4.85(br. s, 2H), 7.3(br. m, 2H), 7.4-7.7(m, 5H),  
8.15(d, 2H).



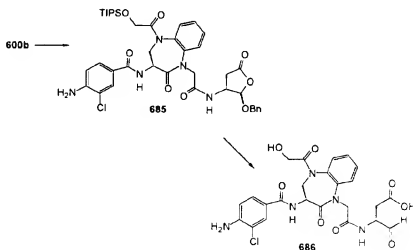
(3*S*)-2-Oxo-3-benzoylamino-5-(2-acetoxy)acetyl-N-  
[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-  
2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetamide  
(682), was synthesized from 600b by the methods used to  
prepare 655 from 600b to afford 495 mg of 682 as a  
white solid, <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.00(s, 3H), 2.05(s, 3H),  
2.47(d, 1H), 2.58(dd, 1H), 2.85(dd, 1H), 2.89(dd, 1H),  
3.9(m, 2H), 4.05-4.15(m, 2H), 4.19(dd, 1H), 4.45(m,  
2H), 4.55-5.05(m, 8H), 5.55(d, 1H), 6.85(d, 1H),  
7.15(d, 1H), 7.25-7.55(m, 10H), 7.75(d, 2H).

(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylamino-5-(2-acetoxy)acetyl-  
2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-  
acetyl-amino]4-oxo-butyric acid (683), was synthesized  
from 682 by the method used to prepare 2002 from 2001  
to afford 82 mg of 683 as a white solid, <sup>1</sup>H NMR (CD<sub>3</sub>OD)  
δ 2.1(s, 3H), 2.5(m, 1H), 2.68(m, 1H), 3.8(m, 1H),  
4.29(dd, 1H), 4.31(m, 1H), 4.45(d, 1H), 4.55(d, 1H),  
4.6(d, 1H), 4.72(d, 1H), 4.95(br. s, 2H), 7.45(br. m,  
2H), 7.52-7.65(br. m, 5H), 7.88(d, 2H).

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(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dimethyl-4-methoxybenzoyl)amino-5-acetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetylaminobutyl]butyric acid (684), was synthesized from 600b by the method used to  
 5 prepare 605d from 600b to afford 72 mg of 684 as a white solid,  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  1.9(s, 3H), 2.25(s, 6H), 2.45(m, 1H), 2.6(m, 1H), 3.3(s, 1H), 3.7(s, 3H), 4.25(m, 1H), 4.45-4.6(m, 3H), 7.4(br. s, 2H), 7.55(br. d, 4H).

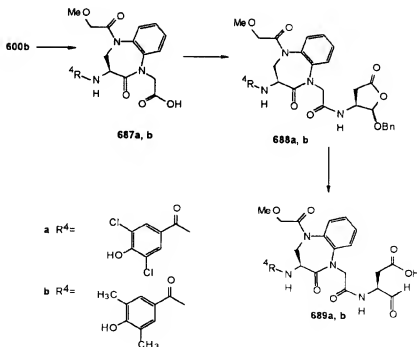


10 (3*S*)-2-Oxo-3-(3-chloro-4-aminobenzoyl)amino-5-(2-triisopropylsilyloxy)acetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1*H*-1,5-

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benzodiazepine-1-acetamide (685), was synthesized from 600b by the methods used to prepare 676 from 600b to afford 165 mg of 685.

(3S)-3-[(3S)-2-Oxo-3-(3-chloro-4-aminobenzoyl)amino-5-(2-triisopropylsilyloxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetyl-amino]4-oxo-butyrac acid (686). To a solution of 685 (165 mg, 0.21 mmol) in THF was added a solution of TBAF (1M, 0.21 mL). The product was isolated by filtration after precipitation from reaction mixture. Reverse phase chromatography (10% to 80% MeCN in water/ 0.1% TFA) afforded 25 mg of 686 as a white solid,  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  2.37-2.42 (m), 2.59-2.70 (m), 3.60-3.89 (m), 4.01 (d), 4.20-4.31 (m), 4.42-4.70 (m), 4.80-5.05 (m), 6.79 (d), 7.32-7.65 (m), 7.81 (s).



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(3S)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid (687a), was synthesized from 600b using methods similar to those used for preparing 654 from 5 600b to afford 1.6 g of 687a.

(3S)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid (687b), was synthesized from 600b using methods similar to those used for preparing 654 from 10 600b to afford 1.1 g of 687b.

(3S)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-methoxyacetyl-N-[(2RS,3S)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (688a). To a solution of 15 (3S,2R,S)-3-allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydrofuran (Chapman, Biorg. Med. Chem. Lett., 2, pp. 613-618 (1992)) (1.13 g, 1.2 equiv) in CH<sub>2</sub>Cl<sub>2</sub> was added triphenylphosphine (423 mg, 0.5 equiv), dimethylbarbituric acid (1.26 g, 2.5 equiv), and 20 tetrakis(triphenylphosphine) palladium (0) (373 mg, 0.1 equiv). After 5 minutes the reaction mixture was cooled via ice-bath then added a solution of 687a in DMF (1.6 g, 1 equiv), HOBt (460 mg, 1.1 equiv), and EDC (681 mg, 1.1 equiv). The resulting mixture was allowed 25 to stir at ambient temperature. After 16 hours the reaction mixture was poured into NaHSO<sub>4</sub> and extracted twice with EtOAc. The organic layer was washed with NaHCO<sub>3</sub>, brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. Chromatography (SiO<sub>2</sub>, 20% to 100% EtOAc in 30 CH<sub>2</sub>Cl<sub>2</sub>) afforded 880mg of 688a as an off-white solid, <sup>1</sup>H

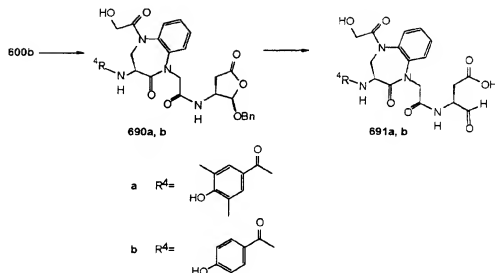
- 704 -

NMR (CD<sub>3</sub>OD)  $\delta$  2.55(dd, 1H), 2.7(dd, 1H), 3.0(m, 1H), 3.6(m, 1H), 3.75(d, 1H), 3.9-4.0(m, 2H), 4.3-4.45(m, 3H), 4.5-4.6(m, 3H), 4.7(m, 2H), 5.35(s, 1H), 5.55(d, 1H), 7.1-7.5(m, 4H), 7.85(s, 2H).

- 5 (3S)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-methoxyacetyl-N-[(2RS,3S)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (688b), was synthesized from 687b by the method used to prepare 688a from 687a to
- 10 afford 960 mg of 688b as an off-white solid, <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  2.6(dd, 1H), 2.7(dd, 1H), 3.0(dd, 1H), 3.2(s, 3H), 3.7(m, 3H), 3.9(m, 2H), 4.4-4.5(m, 2H), 4.6(m, 3H), 5.35(s, 1H), 5.55(d, 1H), 7.25(m, 2H), 7.4-7.5(m, 4H).
- 15 (3S)-3-[(3S)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (689a), was synthesized from 688a by the method used to prepare 2002 from 2001 to afford 184 mg
- 20 of 689a as a white solid, <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  2.45(m, 1H), 2.6(m, 1H), 3.3(s, 3H), 3.7-3.85(m, 2H), 4.0(d, 1H), 4.3(m, 1H), 4.5-4.6(m, 3H), 7.3-7.6(m, 4H), 7.85(s, 2H).
- 25 (3S)-3-[(3S)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (689b), was synthesized from 688b by the method used to prepare 2002 from 2001 to afford 412 mg of 689b as a white solid, <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  2.5(m, 1H),

- 705 -

2.7 (m, 1H), 3.3 (s, 3H), 3.7-3.85 (m, 2H), 4.05 (dd, 1H),  
4.3 (m, 1H), 4.6 (m, 2H), 7.45-7.4 (m, 2H), 7.5 (s, 2H),  
7.55 (m, 2H).



- (3S)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-hydroxyacetyl-N-[(2RS,3S)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (690a), was synthesized from 600b via methods used to prepare 676 from 600b, 688a from 687a, then 677 from 676 to afford 863 mg of 690a as a white solid,  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  2.2 (s, 6H), 2.45 (d, 0.5H), 2.6-2.9 (m, 1H), 3.05 (dd, 0.5H), 3.65-3.85 (m, 2H), 3.95-4.1 (m, 1H), 4.35-5.0 (m, 7H), 5.35 (s, 0.5H), 5.65 (d, 0.5H), 7.2-7.4 (m, 4H), 7.4-7.7 (m, 7H).

- (3S)-2-Oxo-3-(4-hydroxybenzoyl)amino-5-hydroxyacetyl-N-[(2RS,3S)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (690b), was synthesized from 600b via methods used to prepare 677 from 600b to afford 200 mg of 690b,  $^1\text{H}$  NMR

- 706 -

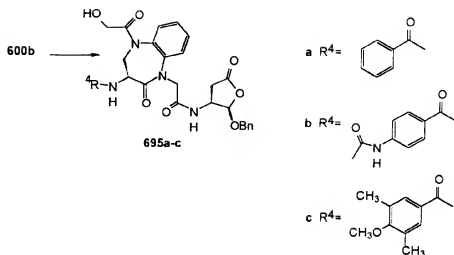
(CD<sub>3</sub>OD)  $\delta$  2.49(d, 1H), 2.65(d, 1H), 2.66(d, 1H), 2.85(d, 1H), 2.87(d, 1H), 3.05(dd, 1H), 3.35(br. s, 1H), 3.72(br. s, 2H), 4.01(m, 2H), 4.45(br. m, 1H), 4.6(m, 1H), 4.7(m, 1H), 4.8(m, 1H), 4.95(br. s, 2H), 5.65(d, 1H), 6.8(d, 2H), 7.2-7.35(br. m, 3H), 7.45(m, 2H), 7.75(d, 2H).

(3S)-3-[(3S)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-hydroxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyr  
10 ic acid (691a), was synthesized from 690a by the method used to prepare 2002 from 2001 to afford 560 mg of 691a as a white solid, <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  2.15(s, 6H), 2.45(m, 1H), 2.65(m, 1H), 3.55(m, 1H), 3.7(d, 1H), 4.0(d, 1H), 4.25(m, 1H), 4.5-4.6(m, 3H), 7.3-7.5(m,  
15 6H).

(3S)-3-[(3S)-2-Oxo-3-(4-hydroxybenzoyl)amino-5-hydroxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyr  
ic acid (691b), was synthesized from 690b by the method used to prepare  
20 2002 from 2001 to afford 410 mg of 691b as a white solid, <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  2.5(m, 1H), 2.65(m, 1H), 3.75(m, 1H), 3.8(d, 1H), 4.05(d, 1H), 4.25(m, 1H), 4.5(m, 1H), 4.6(m, 1H), 4.95(br. s, 2H), 6.8(d, 2H), 7.45(m, 2H), 7.6(m, 2H), 7.75(d, 2H).



- 707 -



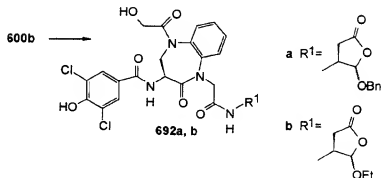
(3S)-2-Oxo-3-benzoylamino-5-hydroxyacetyl-N-[(2RS,3S)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (695a), was synthesized from 600b via methods used to prepare

- 5 677 from 600b to afford 75 mg of 695a, <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 2.2(s, 6H), 2.45(m, 1H), 2.6(m, 1H), 3.65(m, 1H), 3.75(d, 1H), 4.0(d, 1H), 4.28(m, 1H), 4.5(m, 3H), 7.4-7.6(m, 6H).

- (3S)-2-Oxo-3-(4-acetamidobenzoyl)amino-5-hydroxyacetyl-N-[(2RS,3S)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (695b), was synthesized from 600b via methods used to prepare 677 from 600b to afford 880 mg of 695b, <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.1(s, 3H), 2.25-2.5(m, 2H), 2.8-2.92(m, 0.5H), 3.15-3.2(m, 0.5H), 3.45-3.6(m, 2H), 3.75-3.95(m, 2H), 4.15-4.25(m, 1H), 4.35-4.6(m, 2H), 4.6-4.88(m, 3H), 5.22(s, 0.25H), 5.33(s, 0.25H), 5.52-5.58(d, 0.5H), 7.15-7.45(m, 9.5H), 7.5-7.75(m, 5H), 8.3-8.35(m, 0.5H), 9.08-9.18(m, 1H).

- 708 -

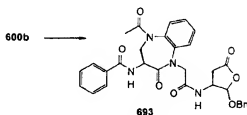
(3*S*)-2*RS*-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-hydroxyacetyl-N-(2-benzyloxy-5-oxo-tetrahydrofuran-3-yl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetamide (**695c**), was synthesized from **600b** via methods used to prepare **677** from **600b** to afford 840 mg of **695c**,  
<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 2.23(s, 3H), 2.26(s, 3H), 2.45-2.62(m, 1H), 2.8-2.9(dd, 0.5H), 2.9-3.05(dd, 0.5H), 3.45-3.63(m, 1H), 3.64(s, 1.5H), 3.68(s, 1.5H), 3.78-4.05(m, 2H), 4.2-4.33(m, 1H), 4.4-4.63(m, 2H), 4.65-4.94(m, 2H), 4.95-5.1(m, 1H), 5.45(s, 0.5H), 5.5-5.6(d, 0.5H), 6.9-6.95(d, 1H), 7.25-7.7(m, 12H).



(3*S*)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-hydroxyacetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetamide (**692a**), was synthesized from **600b** via methods used to prepare **661** from **600b**, excluding steps used to make **604d** from **603d**, using instead the method to prepare **688a** from **687a** to afford 854 mg of **692a**,  
<sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 2.45(d, 1H), 2.6(m, 1H), 2.7(m, 1H), 3.0(m, 1H), 3.5-3.7(m, 4H), 4.0(q, 2H), 4.45(m, 3H), 4.55(m, 4H), 5.35(s, 1H), 5.6(d, 1H), 7.2-7.5(m, 9H), 7.85(s, 2H).

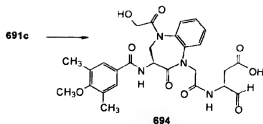
- 709 -

(3*S*)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-hydroxyacetyl-N-[(2*RS*,3*S*)-ethoxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetamide (**692b**), was synthesized from **600b** via methods used to prepare **661** from **600b**, excluding steps used to make **604d** from **603d**, using instead the method to prepare **688a** from **687a** to afford 207 mg of **692b**, <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 1.05(t, 3H), 1.15(t, 3H), 2.45(d, 1H), 2.55(m, 1H), 2.7(m, 1H), 3.55(m, 2H), 3.6-3.75(m, 5H), 4.0(dd, 2H), 4.3(d, 1H), 4.4-4.7(m, 5H), 5.25(s, 1H), 5.5(d, 1H), 7.25-7.6(m, 4H), 7.85(s, 2H).



(3*S*)-2-Oxo-3-benzoylamino-5-acetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetamide (**693**), was synthesized from **600b** via methods used to prepare **688a** from **600b** to afford 30 mg of **693**, <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 1.7(s, 3H), 1.8(s, 3H), 2.51(d, 1H), 2.6(m, 1H), 2.85(m, 1H), 3.0(m, 1H), 3.75(br. d, 2H), 4.0-4.1(dd, 2H), 4.5-5.0(m, 6H), 5.45(s, 1H), 5.55(s, 1H), 7.15-7.85(m, 14H).

- 710 -

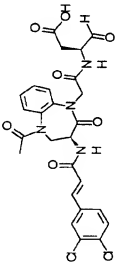
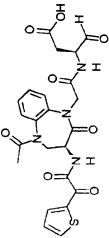


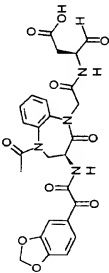
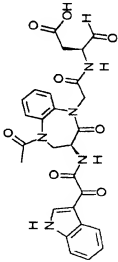
(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dimethyl-4-methoxybenzoyl)amino-5-hydroxyacetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetylamino]4-oxobutyric acid (**694**), was synthesized from **691c** by the  
 5 method used to prepare **2002** from **2001** to afford 380 mg of **694** as a white solid,  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  2.25(s, 6H), 2.45(m, 1H), 2.65(m, 1H), 3.65(m, 5H), 4.0(d, 1H), 4.28(m, 1H), 4.55(d, 2H), 4.95(m, 1H), 7.4-7.6(m, 6H).

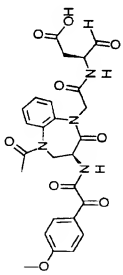
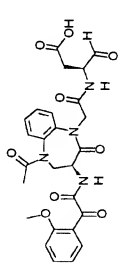
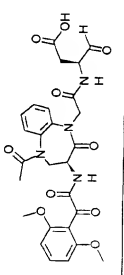
Compounds **700-711** were prepared by methods  
 10 similar to the methods used to prepare compounds **619-635** (see, Example 13). Physical data for compounds **700-711** is listed in Table 25.

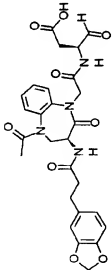
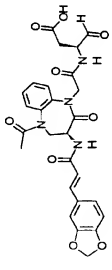
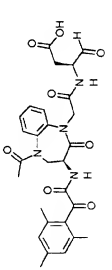
Compounds **910-915** and **918-921** were prepared as described below. Physical data for these compounds is  
 15 listed in Table 26.

Table 25

| Compound | Structure  | MF  | MW     | HPLC RT min<br>(method)<br>Purity | MS<br>(M-Na) + |
|----------|--|---|--------|-----------------------------------|----------------|
| 700      |  | C <sub>26</sub> H <sub>24</sub> Cl <sub>2</sub> N <sub>4</sub> O <sub>7</sub> | 575.41 | 14.061 (2)<br>97%                 | 600            |
| 701      |  | C <sub>23</sub> H <sub>22</sub> N <sub>4</sub> O <sub>8</sub> S               | 514.52 | 15.589 (1)<br>97%                 | 538.8          |

| Compound | Structure  | MF          | MW     | HPLC RT min<br>(method)<br>Purity | MS<br>(M+Na) <sup>+</sup> |
|----------|--|-------------|--------|-----------------------------------|---------------------------|
| 702      |  | C26H24N4O10 | 552.50 | 15.855 (1)<br>98%                 | 575.9                     |
| 703      |  | C27H25N5O8  | 547.53 | 10.315 (2)<br>97%                 | 572.1                     |

| Compound | Structure  | MF   | MW     | HPLC RT min<br>(method)<br>Purity | MS<br>(M+Na) + |
|----------|--|--|--------|-----------------------------------|----------------|
| 704      |  | C <sub>26</sub> H <sub>26</sub> N <sub>4</sub> O <sub>9</sub>  | 538.52 | 10.475 (2)<br>96%                 | 562.1          |
| 705      |  | C <sub>26</sub> H <sub>26</sub> N <sub>4</sub> O <sub>9</sub>  | 538.52 | 14.260 (1)<br>72%                 | 562.1          |
| 706      |  | C <sub>27</sub> H <sub>28</sub> N <sub>4</sub> O <sub>10</sub> | 568.55 | 14.836 (1)<br>97%                 | 592.4          |

| Compound | Structure  | MF         | MW     | HPLC RT min<br>(method)<br>Purity | MS<br>(M+Na) + |
|----------|--|------------|--------|-----------------------------------|----------------|
| 707      |  | C27H28N4O9 | 552.55 | 15.952 (1)<br>98%                 | 575.9          |
| 708      |  | C27H26N4O9 | 550.53 | 10.731 (2)<br>93%                 | 574.6          |
| 709      |  | C28H30N4O8 | 550.57 | 13.192 (2)<br>95%                 | 574            |



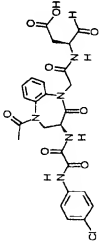
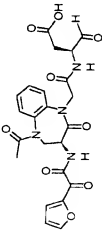
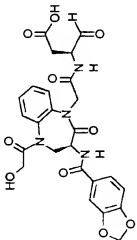
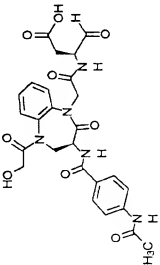
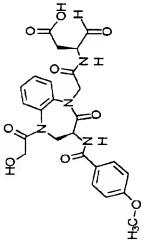
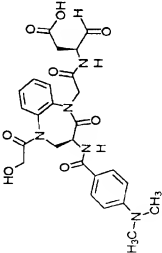
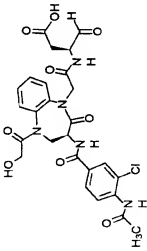
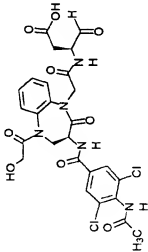
| Compound | Structure  | MF           | Mw     | HPLC RT min<br>(method)<br>Purity | MS<br>(M+Na) <sup>+</sup> |
|----------|--|--------------|--------|-----------------------------------|---------------------------|
| 710      |  | C25H24ClN5O8 | 557.95 | 12.406 (2)<br>98%                 | 582.2                     |
| 711      |  | C23H22N4O9   | 498.45 | 13.072 (1)<br>99%                 | 521.9                     |

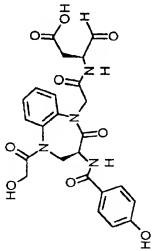
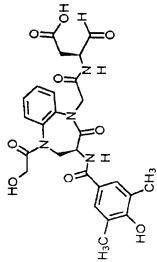
Table 26

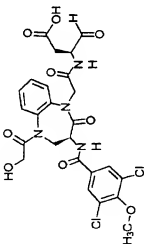
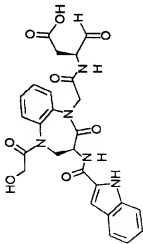
| Compound | Structure  | MF          | MW     | HPLC RT min<br>(method)<br>Purity | MS<br>(M+Na) + |
|----------|--|-------------|--------|-----------------------------------|----------------|
| 910      |  | C25H24N4O10 | 540.49 | 8.172 (2)<br>99%                  | 564.4          |
| 911      |  | C26H27N5O9  | 553.53 | 6.949 (2)<br>99%                  | 577.5          |

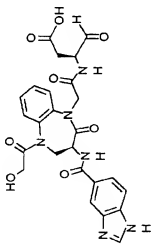
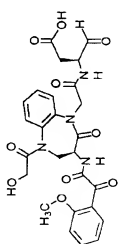
- 717 -

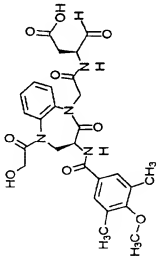
| Compound | Structure  | MF         | MW     | HPLC RT min<br>(method)<br>Purity | MS<br>(M+Na) <sup>+</sup> |
|----------|--|------------|--------|-----------------------------------|---------------------------|
| 912      |  | C25H26N4O9 | 526.51 | 8.317 (2)<br>99%                  | 550.7                     |
| 913      |  | C26H29N5O8 | 539.55 | 6.588 (2)<br>99%                  | 563.5                     |

| Compound | Structure  | MF            | MW     | HPLC RT min<br>(method)<br>Purity | MS<br>(M+Na) + |
|----------|--|---------------|--------|-----------------------------------|----------------|
| 914      |  | C26H26ClN5O9  | 587.98 | 7.815 (2)<br>99%                  | 612.2          |
| 915      |  | C26H25Cl2N5O9 | 622.42 | 7.490 (?)<br>98%                  | 647            |

| Compound | Structure  | MF  | NW     | HPLC R <sub>t</sub> min<br>(method)<br>Purity | MS<br>(M+Na) + |
|----------|--|---|--------|---|----------------|
| 916/691b |  | C <sub>24</sub> H <sub>24</sub> N <sub>4</sub> O <sub>9</sub> | 512.48 | 6.331 (2)<br>98%                              | 537            |
| 917/691a |  | C <sub>26</sub> H <sub>28</sub> N <sub>4</sub> O <sub>9</sub> | 540.53 | 8.114 (2)<br>99%                              | 564.9          |

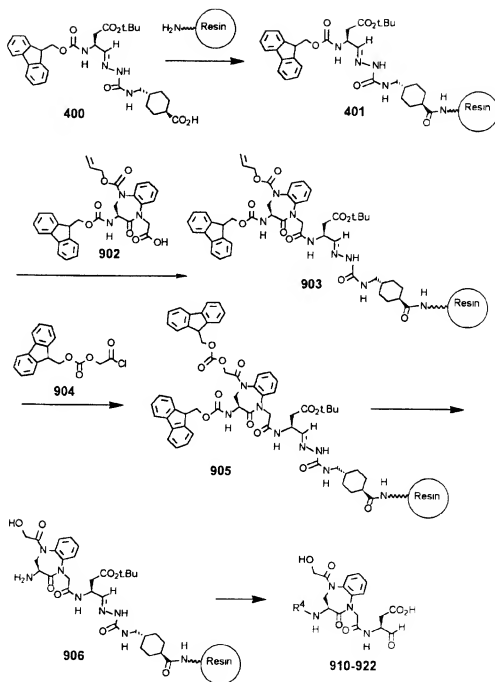
| Compound | Structure  | MF            | NW     | HPLC RT min<br>(method)<br>Purity | MS<br>(M+Na) <sup>+</sup> |
|----------|--|---------------|--------|-----------------------------------|---------------------------|
| 918      |  | C25H24Cl2N4O9 | 595.40 | 11.817 (2)<br>99%                 | 619.3                     |
| 919      |  | C26H25N5O8    | 535.52 | 9.709 (2)<br>91%                  | 559.7                     |

| Compound | Structure  | MF          | MW     | HPLC RT min<br>(method)<br>Purity | MS<br>(M+Na) + |
|----------|--|-------------|--------|-----------------------------------|----------------|
| 920      |  | C25H24N6O8  | 536.51 | 5.494 (2)<br>98%                  | 560.6          |
| 921      |  | C26H26N4O10 | 554.52 | 7.827 (2)<br>96%                  | 579.1          |

| Compound | Structure  | MF         | MW     | HPLC Rt min<br>(method)<br>Purity | MS<br>(M+Na) + |
|----------|--|------------|--------|-----------------------------------|----------------|
| 922/694  |  | C27H30N4O9 | 554.56 | 10.024 (2)<br>99%                 | 578.8          |



- 723 -



- 724 -

**Step A. Synthesis of 401.** TentaGel S $\text{NH}_2$  resin (0.25 mmol/g, 6.8 g) was placed in a glass shaker vessel and washed with dimethylacetamide (3 X 20 mL). To a solution of **400** (1.70 g, 2.9 mmol, prepared from

5 (3S) 3-(fluorenylmethoxycarbonyl)-4-oxobutryic acid t-butyl ester according to A.M. Murphy et. al. J. Am. Chem. Soc., 114, 3156-3157 (1992)) in dimethylacetamide (15 mL) was added O-benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU; 1.09 g,

10 2.9 mmol), and DIEA (1.0 mL, 5.7 mmol). The solution was added to the resin, followed by dimethylacetamide (5 mL). The reaction mixture was agitated for 3 h at room temperature using a wrist arm shaker. The resin was isolated by suction filtration and washed with

15 dimethylacetamide (6 X 20 mL). A sample of resin (7.4 mg) was thoroughly washed with 50% methanol in dichloromethane and dried under suction. Deprotection of the Fmoc group using 20% piperidine in dimethylacetamide (10.0 mL) and UV analysis of the

20 solution revealed a substitution of  $0.19 \text{ mmol g}^{-1}$ .

**Step B. Synthesis of 903.** Resin **401** was deprotected with 20% (v/v) piperidine/dimethylacetamide (20 mL) for 10 min (shaking) and then for 10 min with

25 fresh piperidine reagent (20 mL). The resin was then washed with dimethylacetamide (6 X 20 mL). A solution of **902** (1.52 g, 2.81 mmol) was treated with HBTU (1.07 g, 2.83 mmol) and DIEA (1.0 mL, 5.7 mmol) and transferred to the resin, followed by dimethylacetamide

30 (5 mL). The reaction mixture was agitated for 2.5 h at room temperature using a wrist arm shaker. The resin was isolated by suction filtration and washed with

- 725 -

dimethylacetamide (4 X 20 mL) and dichloromethane (4 X 20 mL), and dried under nitrogen purge. Resin substitution was performed as described for 401 and determined to be 0.169 mmol g<sup>-1</sup>.

5

**Step C. Synthesis of 905.** Resin 903 (7.54 g, 1.27 mmol) and dimedone (2.19 g, 15.6 mmol) were placed in a 100 mL round bottomed flask and freshly distilled anhydrous tetrahydrofuran (60 mL) was added.

10 Tetrakis(triphenylphosphine)palladium (0) (0.32 g, 0.28 mmol) was added and the nitrogen blanketed, sealed reaction was agitated for 15 h on a wrist action shaker. The resin was filtered, washed with

15 dimethylacetamide (4 X 20 mL), dichloromethane (4 X 20 mL) and dimethylacetamide (1 X 20 mL). Sufficient dimethylacetamide was added to the resin to obtain a slurry followed by pyridine (1.5 mL, 18.5 mmol) and a solution of 904 (5.5 mmol) in dichloromethane (10 mL). The reaction was shaken under nitrogen for 8 h, then

20 filtered. The resin was washed with dimethylacetamide (5 X 20 mL) and dichloromethane (5 X 20 mL).

**Step D. Synthesis of 906.** This compound was prepared from resin 905 (0.24 g, 0.038 mmol) using an

25 Advanced ChemTech 396 Multiple Peptide synthesizer. The automated cycles consisted of a resin wash with dimethylformamide (3 X 1 mL), deprotection with 25% (v/v) piperidine in dimethylformamide (1 mL) for 10 min followed by fresh reagent (1 mL) for 20 min to yield

30 resin 906. The resin was washed with dimethylformamide (3 X 1 mL) and N-methylpyrrolidone (3 X 1 mL).

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**Step E. (910-922)** Resin 906 was acylated with a solution of 0.4M carboxylic acid and 0.4M HOBT in N-methylpyrrolidone (0.5 mL), a solution of 0.4M HBTU in N-methylpyrrolidone (0.5 mL) and a solution of 1.6M DIEA in N-methylpyrrolidone (0.25 mL) and the reaction was shaken for 2 hr at room temperature. The resin was washed with N-methylpyrrolidone (1 X 1 mL), dimethylformamide (4 X 1 mL), 50% methanol in dichloromethane (5 X 1 mL) and dried in air. The aldehyde was cleaved from the resin and globally deprotected by treatment with 95% TFA/ 5% H<sub>2</sub>O (v/v, 1.5 mL) for 30 min at room temperature. After washing the resin with cleavage reagent (2 X 1 mL), the combined filtrates were added to cold 1:1 ether:hexane (35 mL) and the resulting precipitate was isolated by centrifugation and decantation. The resulting pellet was dissolved in acetonitrile (0.5 mL) and H<sub>2</sub>O (0.5 mL) and filtered through 0.45 micron microcentrifuge filters. The compound was purified by semi-preparative RP-HPLC with a Rainin Microsorb<sup>TM</sup> C18 column (5  $\mu$ , 21.4 X 250 mm) eluting with a linear acetonitrile gradient (10% - 50%) containing 0.1% TFA (v/v) over 30 min at 12 mL/min. Fractions containing the desired product were pooled and lyophilized to provide 910-922.

25

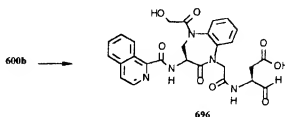
**Analytical HPLC methods:**

(1) Waters DeltaPak C18, 300Å (5 $\mu$ , 3.9 X 150 mm).  
Linear acetonitrile gradient (0% - 25%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.

- 727 -

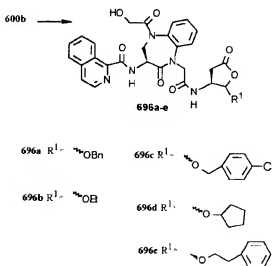
(2) Waters DeltaPak C18, 300Å (5μ, 3.9 X 150 mm).

Linear acetonitrile gradient (5% - 45%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.



(3S)-3-[(3S)-2-Oxo-3-(isoquinolin-1-oyl)amino-5-

5 hydroxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyrac acid (696) was synthesized from 600b by the method used to prepare 691a from 600b to afford 696.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  2.45(m, 1H), 2.7(m, 1H), 3.75(d, 1H), 3.95(q, 1H), 4.05(d, 1H), 4.3(m, 1H), 4.45-4.65(m, 2H), 5.05(m, 1H), 7.5-7.6(m, 3H), 7.7(t, 1H), 7.8(t, 1H), 7.98(t, 1H), 8.55(d, 1H), 9.1(d, 1H).



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(3S)-2-Oxo-3-(isoquinolin-1-yl)amino-5-hydroxyacetyl-N-[(2RS,3S)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (696a) was synthesized from 600b via methods used to  
5 prepare 690a from 600b to afford 696a. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.95(t, 2H), 1.25(t, 1H), 1.4(m, 2H), 1.55(m, 1H), 2.55(m, 1H), 2.85(m, 1H), 2.95(dd, 1H), 3.15(m, 1H), 3.55(m, 1H), 3.9(m, 2H), 4.35(t, 1H), 4.4-4.55(m, 2H), 4.75(m, 1H), 4.8-5.05(m, 2H), 5.45(s, 1H), 5.55(d, 1H),  
10 6.85(d, 1H), 7.15(d, 1H), 7.2-7.5(m, 5H), 7.6-7.8(m, 3H), 8.45(d, 1H), 9.05(d, 1H), 9.35(d, 1H).

(3S)-2-Oxo-3-(isoquinolin-1-yl)amino-5-hydroxyacetyl-N-[(2RS,3S)-ethoxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-carboxamide (696b)  
15 was synthesized from 600b via methods used to prepare 690a from 600b to afford 696b. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.9(m, 3H), 1.15(q, 3H), 1.15(m, 1H), 1.65(m, 1H), 2.5(m, 1H), 2.8(m, 1H), 2.95-3.0(m, 2H), 3.6(m, 2H), 3.7-3.85(m, 4H), 4.0(m, 2H), 4.3(m, 1H), 4.55(m, 1H), 4.65(m, 1H),  
20 4.85-4.95(m, 1H), 5.05(m, 1H), 5.35(s, 1H), 5.45(d, 1H), 6.85(d, 1H), 7.25(d, 1H), 7.35-7.85(6H), 8.85(dd, 2H), 9.05(m, 1H), 9.35(dd, 2H).

(3S)-2-Oxo-3-(isoquinolin-1-yl)amino-5-hydroxyacetyl-[2RS-(4-chlorobenzyl)oxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-carboxamide (696c) was synthesized from 600b via methods used to  
25 prepare 690a from 600b to afford 696c. <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 1.25(t, 1H), 1.65(q, 1H), 1.9(m, 1H), 2.9(m, 1H),

- 729 -

3.05(m, 1H), 3.9(d, 1H), 4.2(m, 1H), 4.3(d, 1H), 4.7-5.0(m, 3H), 5.25(m, 1H), 5.7(s, 1H), 5.9(d, 1H), 7.5(d, 2H), 7.7-7.9(m, 3H), 8.0(t, 1H), 8.2(m, 2H), 8.75(d, 1H), 9.35(d, 1H).

- 5 (3S)-2-Oxo-3-(isoquinolin-1-yl)amino-5-hydroxyacetyl-(2RS-cyclopentyl-oxy-5-oxo-tetrahydrofuran-3-yl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-carboxamide (696d) was synthesized from 600b via methods used to prepare 690a from 600b to afford 696d. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ
- 10 0.9(t, 1H), 1.2(t, 1H), 1.3-1.45(m, 2H), 1.6-1.8(m, 4H), 2.45(m, 1H), 2.8(m, 1H), 3.0(m, 1H), 3.4(q, 1H), 3.5(d, 1H), 4.0(m, 2H), 4.2-4.3(m, 2H), 4.55(d, 1H), 4.65(m, 1H), 4.9(m, 1H), 5.05(m, 1H), 5.4(s, 1H), 5.5(d, 1H), 6.8(d, 1H), 7.3-7.9(m, 6H), 8.5(d, 1H),
- 15 9.05(d, 1H), 9.4(d, 1H).

- (3S)-2-Oxo-3-(isoquinolin-1-yl)amino-5-hydroxyacetyl-N-[(2R,3S)-phenethoxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (696e) was synthesized from 600b via methods used to
- 20 prepare 690a from 600b to afford 696e. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ
- 1.2(t, 1H), 2.4(m, 1H), 2.8(m, 2H), 3.6(d, 1H), 3.7(q, 1H), 4.0(m, 2H), 4.3(d, 2H), 4.65(m, 1H), 4.85(t, 1H), 5.0(m, 1H), 5.35(d, 1H), 6.5(d, 1H), 7.15-7.85(m, 8H), 8.45(d, 1H), 9.05(d, 1H), 9.4(d, 1H).

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Example 32Table 27

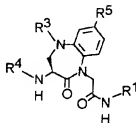
| Compound | UV-Visible<br>Ki (nM) | Cell<br>PBMC<br>avg.<br>IC50<br>(nM) | Whole<br>human<br>blood<br>IC50<br>(nM) | Clearance<br>Mouse,<br>i.v.<br>ml/min/kg | Clearance<br>Rat, i.v.<br>ml/min/kg |
|----------|-----------------------|--------------------------------------|---|--|-------------------------------------|
| 688c     | 200                   |                                      |   |  |                                     |
| 5 689b-1 | 3.5                   |                                      | 2700                                    |  |                                     |
| 696-1    | 0.5                   |                                      |   |  |                                     |
| 696-2    | 0.5                   |                                      |   |  |                                     |
| 697      | 1.8                   |                                      | 5000                                    |  |                                     |
| 698      | 18                    |                                      | 13500                                   |  |                                     |
| 10 699   | 1.1                   |                                      |   |  |                                     |
| 699a-2   |                       |                                      |   |  |                                     |
| 720      | 2.7                   |                                      |   |  |                                     |
| 721      | 1.3                   |                                      | 5000                                    |  |                                     |
| 722      | 5                     |                                      | 5000                                    |  |                                     |
| 15 723   | 2.3                   |                                      | 2000                                    |  |                                     |
| 724      | 2                     |                                      | 1800                                    |  |                                     |
| 725      | 3.7                   |                                      | 3000                                    |  |                                     |
| 726      | 300                   |                                      |   |  |                                     |
| 727      | 50                    |                                      | 2300                                    |  |                                     |
| 20 728   | 300                   |                                      |   |  |                                     |
| 729      | 28                    |                                      | 2800                                    |  |                                     |
| 730      | 90                    |                                      | 8000                                    |  |                                     |
| 731      | 150                   |                                      |   |  |                                     |
| 732      | 5                     |                                      | 1800                                    |  |                                     |
| 25 733   | 5                     |                                      | 1500                                    |  |                                     |
| 734      | 9                     |                                      | 6000                                    |  |                                     |
| 735      | 6                     |                                      | 10000                                   |  |                                     |



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Example 33































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Table 28

| CIP#   | R <sup>4</sup> | R <sup>3</sup> | R <sup>5</sup> | R <sup>1</sup> |
|--------|----------------|----------------|----------------|----------------|
| 684a   |                |                | H              |                |
| 688b-1 |                |                | F              |                |
| 688c   |                |                | H              |                |
| 689b-1 |                |                | F              |                |
| 690a-1 |                |                | H              |                |

10













- 732 -

| CIP#   | R <sup>4</sup>  | R <sup>3</sup>  | R <sup>5</sup> | R <sup>1</sup>  |
|--------|---|---|----------------|---|
| 696-1  |    |    | F              |    |
| 696-2  |    |    | Cl             |    |
| 696a-2 |    |    | Cl             |    |
| 696a-1 |    |    | F              |    |
| 697    |    |    | H              |    |
| 697a   |    |    | H              |    |
| 698    |    |    | H              |    |
| 698a   |   |    | H              |   |
| 699    |  |  | H              |  |
| 699a   |  |  | H              |  |

5

10

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| CIP#   | R <sup>4</sup>  | R <sup>3</sup>  | R <sup>5</sup> | R <sup>1</sup>  |
|--------|---|---|----------------|---|
| 699a-1 |  |  | F              |  |
| 699a-2 |  |  | F              |  |
| 800    |  |  | H              |  |
| 801    |  |  | H              |  |

- 5 (3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-hydroxyacetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetyl-amino]4,4-diethoxybutyric acid ethyl ester (690a-1), was synthesized by the methods used to prepare 690a and
- 10 2100b to afford 690a-1, <sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 1.15(t, 6H), 1.3(t, 3H), 2.25(s, 6H), 2.60(d, 2H), 3.50(m, 2H), 3.70(m, 4H), 4.05(m, 2H), 4.15(m, 2H), 4.30(d, 1H), 4.45(m, 1H), 4.50(d, 1H), 4.55(d, 1H), 4.70(t, 1H), 5.05(m, 1H), 5.30(s, 1H), 6.70(d, 1H), 7.10(d, 2H),
- 15 7.30-7.50(m, 7H)

- (3*S*)-2-Oxo-3-(3,5-dichloro-4-aminobenzoyl)amino-5-hydroxyacetyl-N-[(2*RS*,3*S*) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetamide (697a) was synthesized via
- 20 methods used to prepare 677 to afford 840 mg of 697a, <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.78 (br. s, 2H), 2.48-2.58 (d, 0.5H),

- 734 -

2.6-2.7 (m, 0.5H), 2.8-2.9 (m, 0.5H), 2.92-3.03 (m, 0.5H), 3.55-3.8 (m, 2H), 3.92-4.02 (d, 1H), 4.25-4.3 (d, 0.5H), 4.37-4.42 (d, 0.5H), 4.43-4.48 (m, 0.5H), 4.55-4.65 (m, 1.5H) 4.7-5.12 (m, 5H), 5.44 (s, 0.5H),  
5 5.58-5.63 (d, 0.5H), 6.95-8.1 (m, 13H).

(3S)-3-[(3S)-2-Oxo-3-(3,5-dichloro-4-aminobenzoyl)amino-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxobutyric acid (697) was synthesized via methods used to prepare 2002 from 2001 to afford 140 mg  
10 of 697, <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 2.38-2.5 (m, 1H), 2.55-2.75 (m, 1H), 3.68-3.9 (m, 3H), 3.95-4.03 (m, 1H), 4.2-4.3 (m, 1H), 4.4-4.7 (m, 4H), 7.35-7.8 (m, 6H).

(3S)-3-[(3S)-2-Oxo-3-(3,5-dimethyl-4-methoxybenzoyl)amino-5-hydroxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-acetoxy-3-butenic acid ethyl ester (684a), was  
15 synthesized by the methods used to prepare 2100j to afford 684a, <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub> mixture of diastereomers) δ 1.3 (s, 9H), 1.8 (s, 3H), 2.1 (s, 3H),  
20 2.15 (s, 3H), 2.3 (s, 6H), 3.3-3.5 (m, 3H), 3.65 (s, 3H), 3.9 (m, 1H), 4.1 (d, 1H), 4.3 (d, 1H), 4.6-4.8 (m, 3H), 5.0 (m, 1H), 6.7 (s, 1H), 7.0 (d, 1H), 7.1 (d, 1H), 7.2-7.5 (m, 6H).

(3S)-2-Oxo-3-isoquinolin-1-ylamino-5-formyl-N-[(2RS,3S) 2-benzoyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (698a) was synthesized via methods used to  
25 prepare 652 to afford 795 mg of 698a <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub> mixture of diastereomers) δ 2.8 (m, 2H), 4.0 (m, 1H), 4.5-4.8 (m, 4H), 5.2 (m, 1H), 5.5 (s, 1H), 5.75 (d,  
30

- 735 -

1H), 7.3-7.85(m, 11H), 7.9(t, 1H), 8.2(d, 1H), 8.6(m, 1H), 9.3(m, 1H).

(3S)-3-[(3S)-2-Oxo-3-isoquinolin-1-oylamino-5-formyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-

- 5 acetylamino]4-oxobutyric acid(698) was synthesized via methods used to prepare 653 to afford 225 mg of 698 <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 2.4(m, 1H), 2.6(m, 1H), 3.9(m, 1H), 4.2(m, 1H), 4.3-4.7(m, 4H), 5.1(m, 1H), 7.3-7.5(m, 4H), 7.6-7.8(m, 2H), 7.8(m, 2H), 8.2(d, 1H), 8.5(d, 10 1H), 9.0(d, 1H).

(3S)-2-Oxo-3-isoquinolin-1-oylamino-5-methoxyacetyl-N-[(2RS,3S) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-

- 2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide(699a) was synthesized via methods used to 15 prepare 655 to afford 820 mg of 699a as a tan solid, <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 2.60 (ddd, 1H), 2.90 (ddd, 1H), 3.20 (s, 3H), 3.25 (s, 3H), 3.70 (t, 1H), 3.90 (m, 2H), 4.20 (dd, 1H), 4.60 (m, 2H), 4.70-5.00 (m, 5H), 5.55 (d, 1H), 7.00 (d, 1H), 7.20-7.50 (m, 7H), 8.45 (dd, 20 1H), 9.0 (dd, 1H), and 9.35 ppm (dd, 1H).

(3S)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-methoxyacetyl-N-[(2RS,3S) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-7-fluoro-1H-1,5-benzodiazepine-1-acetamide(688b-1) was synthesized

- 25 via methods used to prepare 655 to afford 600 mg of 688b-1, <sup>1</sup>H NMR (CDCl<sub>3</sub>; mix. of diastereomers) δ 2.21 (s, 3H), 2.28 (s, 3H), 2.42-2.50 (m, 0.5 H), 2.58-2.65 (m, 0.5H), 2.83-2.91 (m, 0.5H), 2.98-3.1 (m, 0.5H), 3.18 (s, 1.5H), 3.22 (s, 1.5H), 3.72-3.78 (d, 1H), 3.78-3.9 (m, 2H), 4.08-4.15 (d, 1H), 4.5-4.69 (m, 3H), 4.7-
- 30

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4.85 (m, 1H), 4.88-5.1 (m, 2H), 5.45 (s, 0.5H), 5.55-5.65 (d, 0.5H), 6.85-6.92 (m, 1H), 7.02-7.13 (m, 2H), 7.24-7.55 (m, 9H).

- 5 (3S)-3-[(3S)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-7-fluoro-1H-1,5-benzodiazepine-1-acetyl-amino]4-oxobutyric acid(689b-1) was synthesized via methods used to prepare 2002 from 2001 to afford
- 10 689b-1, <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 2.18 (s, 6H), 2.36-2.47 (m, 1H), 2.6-2.72 (m, 1H), 3.34 (s, 3H), 3.66-3.88 (m, 2H), 3.95-4.05 (m, 1H), 4.2-4.78 (m, 5H), 4.9 (m, 1H), 7.3-7.41 (m, 2H), 7.48 (s, 2H), 7.5-7.63 (m, 1H).

- (3S)-3-[(3S)-2-Oxo-3-isoquinolin-1-ylamino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetyl-amino]4-oxobutyric acid(699) was synthesized via methods used to prepare 2002 from 2001 to afford
- 15 699 as a white solid, <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 2.50 (m, 1H), 2.70 (m, 1H), 3.25 (s, 3H), 3.80 (bd, 1H),
- 20 3.90 (bd, 1H), 4.00 (bd, 1H), 4.30 (m, 1H), 4.50-4.70 (m, 3H), 4.80-4.85 (bt, 1H), 5.00 (bm, 1H), 7.40-7.55 (m, 5H), 7.70 (bm, 1H), 7.85 (br, 1H), 8.00 (bm, 1H), 8.55 (bd, 1H), and 9.05 ppm (bd, 1H).

- (3S)-2-Oxo-3-isoquinolin-1-ylamino-5-hydroxyacetyl-N-[(2RS,3S) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-7-fluoro-1H-1,5-benzodiazepine-1-acetamide(696a-1) was synthesized via methods used to
- 25 prepare 656 to afford 800 as a yellow solid, <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 2.55 (ddd, 1H), 2.85 (ddd, 1H),
- 30 3.70-3.80 (m, 2H), 3.95 (bm, 1H), 4.05 (d, 1H), 4.30 (q, 1H), 4.40-4.60 (m, 4H), 4.70-5.05 (m, 4H), 5.55

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(d, 1H), 7.10 (d, 1H), 7.20-7.35 (m, 3H), 7.40- 7.50 (m, 1H), 7.60- 7.85 (m, 3H), 8.40 (dd, 1H), 9.10 (m, 1H), and 9.30 pp (m, 1H).

- (3S)-2-Oxo-3-isoquinolin-1-oylamino-5-hydroxyacetyl-N-  
5 [(2RS,3S) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-  
2,3,4,5-tetrahydro-7-chloro-1H-1,5-benzodiazepine-1-  
acetamide (696a-2) was synthesized via methods used to  
prepare 677, to afford 204 mg of 696a-2 as a white  
solid, with the exception that the reduction of the  
10 nitro- group was done as follows: To a solution of the  
nitro compound (7.2 g, 20 mmol) in MeOH was added  $\text{NH}_4\text{Cl}$   
(2.1 g, 39 mmol) and Zn (17 g, 260 mmol). The  
resulting mixture was heated to reflux 1 hour after  
which it was cooled and filtered through celite. The  
15 filtrate was concentrated in vacuo then treated with  
cold 1N HCl to afford 3.6 g of a pale red solid.  $^1\text{H}$   
NMR( $\text{CDCl}_3$ )  $\delta$  1.85(s, 1H), 2.45(d, 0.5H), 2.50-2.65(m,  
0.5H), 2.80-2.90(m, 0.5H), 2.90-3.00(m, 0.5H), 3.45(s,  
0.5H), 3.55-3.75(m, 1H), 3.85-4.15(m, 2H), 4.25(d, 1H),  
20 4.40-4.65(m, 2H), 4.70-4.80(m, 0.5H), 4.85-5.15(m, 3H),  
5.40(s, 0.5H), 5.60(d, 0.5H), 7.00(d, 0.5H), 7.15-  
7.90(m, 12.5H), 8.35-8.45(m, 1H), 9.00-9.10(m, 1H),  
9.25-9.40(m, 1H)

- (3S)-3-[(3S)-2-Oxo-3-isoquinolin-1-oylamino-5-  
25 hydroxyacetyl-2,3,4,5-tetrahydro-7-fluoro-1H-1,5-  
benzodiazepine-1-acetylamino]4-oxobutyric acid(696-1)  
was synthesized via methods used to prepare 2002 from  
2001 to afford 140 mg of 696-1 as a white solid,  $^1\text{H}$  NMR  
(500 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  2.50 (m, 1H), 2.70 (m, 1H), 3.85 (d,  
30 1H), 3.95 (m, 1H), 4.10 (d, 1H), 4.35 (m, 1H), 4.50-  
4.60 (m, 2H), 4.80 (bm, 1H), 5.00 (m, 1H), 7.40- 7.48

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(m, 3H), 7.65 (m, 1H), 7.75 (t, 1H), 7.85 (t, 1H), 8.00 (d, 1H), 8.55 (d, 1H), and 9.05 ppm (d, 1H).

(3S)-3-[(3S)-2-Oxo-3-isoquinolin-1-ylamino-5-hydroxyacetyl-2,3,4,5-tetrahydro-7-chloro-1H-1,5-

5 benzodiazepine-1-acetyl amino]4-oxobutyric acid (696-2)

was synthesized via methods used to prepare 2002 from 2001 to afford 250 mg of 696-2 as a white solid, <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 2.40-2.55 (m, 1H), 2.60-2.75 (m, 1H), 3.80-4.00 (m, 2H), 4.05 (d, 1H), 4.20-4.35 (m, 1H), 4.45-

10 4.65 (m, 3H), 4.80-5.10 (m, 2H)

(3S)-2-Oxo-3-isoquinolin-1-ylamino-5-methoxyacetyl-N-[(2R,3S)-2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-7-fluoro-1H-1,5-benzodiazepine-1-acetamide (699a-1) was synthesized via methods used to

15 prepare 655 to afford 699a-1 <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 2.55 (ddd, 1H), 2.90 (ddd, 1H), 3.25 (s, 3H), 3.28 (s, 3H), 3.80 (bt, 2H), 3.95 (bm, 2H), 4.25 (dd, 1H), 4.45-4.90 (m, 3H), 5.60 (d, 1H), 7.05-7.40 (m, 8H), 7.50 (bm, 1H), 7.65-7.85 (m, 2H), 8.45 (d, 1H), 9.1 (m, 20 1H), and 9.35 ppm (m, 1H)

(3S)-3-[(3S)-2-Oxo-3-isoquinolin-1-ylamino-5-methoxyacetyl-2,3,4,5-tetrahydro-7-fluoro-1H-1,5-benzodiazepine-1-acetyl amino]4-oxobutyric acid (699a-2)

was synthesized via methods used to prepare 2002 from 25 2001 to afford 699a-2 <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 2.51 (m, 1H), 2.70 (dt, 1H), 3.31 (bs, 3H), 3.90 (bdt, 1H), 3.95 (bm, 1H), 4.05 (d, 1H), 4.35 (m, 1H), 4.50 (d, 1H), 4.60 (dd, 1H), 4.65 (dt, 1H), 4.80 (m, 1H), 5.05 (m, 1H), 7.35-7.48 (m, 3H), 7.65 (bm, 1H), 7.75 (t,



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1H), 7.82 (t, 1H), 8.05 (d, 1H), 8.55 (d, 1H), and 9.05 ppm (d, 1H).

(3S)-3-[(3S)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxobutyric acid, O-2,6-dichlorobenzyl oxime (688c) was synthesized via methods used to prepare 308d to afford 800, <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 2.2 (s, 6H), 2.58-2.83 (m, 2H), 3.28 (s, 3H), 3.29-3.34 (m, 1H), 3.68-3.80 (m, 2H), 3.95-4.05 (dd, 1H), 4.38-4.48 (dd, 1H), 4.82-5.00 (m, 2H), 5.26-5.36 (m, 2H), 7.22-7.65 (m, 10H).

(3S)-2-Oxo-(2,4-dimethylthiao-5-yl)amino-5-hydroxyacetyl-N-[(2RS,3S) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (800) was synthesized via methods used to prepare 696a-1 to afford 204 mg of 800 as a yellow solid, <sup>1</sup>H NMR(CDCl<sub>3</sub>) (mixture of diastereomers) δ 1.70 (s, 1H), 2.40-2.80 (m, 7H), 2.80-2.90 (m, 0.5H), 2.95-3.05 (m, 0.5H), 3.30-3.35 (m, 0.5H), 3.45-3.55 (m, 0.5H), 3.55-3.65 (m, 1H), 3.80-4.05 (m, 2H), 4.30-4.50 (m, 2H), 4.55-4.65 (m, 1H), 4.75-4.95 (m, 3H), 5.45 (s, 0.5H), 5.55 (d, 0.5H), 6.70 (d, 0.5H), 6.90 (d, 0.5H), 7.15-7.80 (m, 10H).

(3S)-3-[(3S)-2-Oxo-3-(2,4-dimethylthiao-1-oyl)amino-5-hydroxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxobutyric acid (801) was synthesized via methods used to prepare 2002 from 2001 to afford 801.

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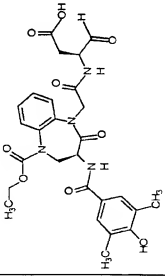
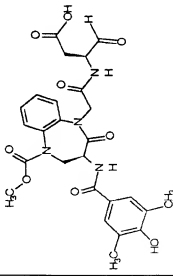
Example 34

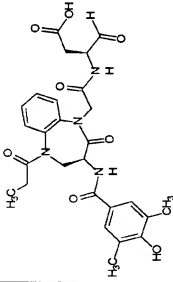
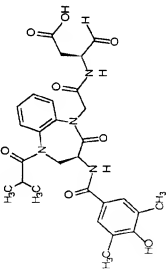
Compounds **720-73** were prepared by methods similar to the methods used to prepare compounds 619-635 (see, Example 13). Physical data for compounds

5 **720-73** is listed in Table 29.

Table 29

| Compound | Structure | MF  | MW     | HPLC RT<br>min<br>Purity | MS<br>(M+Na) <sup>+</sup> |
|----------|-----------|---|--------|--------------------------|---------------------------|
| 720      |           | C <sub>24</sub> H <sub>23</sub> ClN <sub>4</sub> O <sub>9</sub> | 546.93 | 10.729 99%               | 568.8                     |
| 721      |           | C <sub>32</sub> H <sub>32</sub> N <sub>4</sub> O <sub>9</sub>   | 616.63 | 13.241 99%               | 640.4                     |

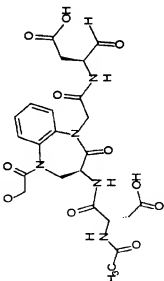
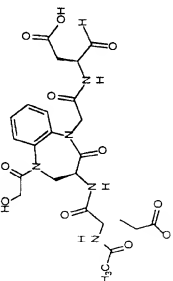
| Compound | Structure  | MF         | MW     | HPLC RT<br>min<br>Purity | MS<br>(M+Na) <sup>+</sup> |
|----------|--|------------|--------|--------------------------|---------------------------|
| 722      |  | C27H30N4O9 | 554.56 | 11.761 99%               | 578.2                     |
| 723      |  | C26H28N4O9 | 540.53 | 10.655 79%               | 564.5                     |

| Compound | Structure  | MF  | MW     | HPLC RT<br>min<br>Purity | MS<br>(M+Na) <sup>+</sup> |
|----------|--|---|--------|--------------------------|---------------------------|
| 724      |  | C <sub>27</sub> H <sub>30</sub> N <sub>4</sub> O <sub>8</sub> | 538.56 | 10.584 99%               | 563.1                     |
| 725      |  | C <sub>28</sub> H <sub>32</sub> N <sub>4</sub> O <sub>8</sub> | 552.59 | 11.329 99%               | 577.2                     |

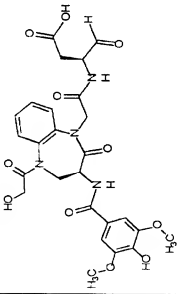
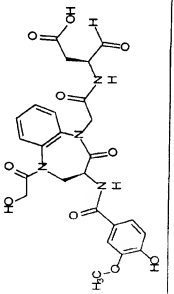
| Compound | Structure | MF   | MW     | HPLC RT<br>min<br>Purity | MS<br>(M+Na) <sup>+</sup> |
|----------|-----------|--|--------|--------------------------|---------------------------|
| 726      |           | C <sub>29</sub> H <sub>32</sub> N <sub>4</sub> O <sub>10</sub> | 596.60 | 10.667 99%               | 620.8                     |
| 727      |           | C <sub>24</sub> H <sub>26</sub> N <sub>4</sub> O <sub>7</sub>  | 482.50 | 9.085 92%                | 506.6                     |

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| Compound | Structure | MF          | MW     | HPLC RT<br>min<br>Purity | MS<br>(M+Na) + |
|----------|-----------|-------------|--------|--------------------------|----------------|
| 728      |           | C30H34N4O10 | 610.63 | 11.556                   | 634.9          |
| 729      |           | C28H30N4O10 | 582.57 | 11.611 99%               | 607.3          |

| Compound | Structure  | MF          | MW     | HPLC RT<br>min<br>Purity | MS<br>(M+Na) + |
|----------|--|-------------|--------|--------------------------|----------------|
| 730      |  | C23H27N5O11 | 549.50 | 3.939 96%                | 572.2          |
| 731      |  | C24H29N5O11 | 563.53 | 4.298 92%                | 587            |



| Compound | Structure  | MF          | MW     | HPLC RT<br>min<br>Purity | MS<br>(M+Na) <sup>+</sup> |
|----------|--|-------------|--------|--------------------------|---------------------------|
| 732      |  | C26H28N4O11 | 572.53 | 7.640 98%                | 595.9                     |
| 733      |  | C25H26N4O10 | 542.51 | 7.375 98%                | 565.9                     |

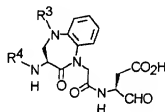
| Compound | Structure | MF          | MW     | HPLC RT<br>min<br>Purity | MS<br>(M+Na) <sup>+</sup> |
|----------|-----------|-------------|--------|--------------------------|---------------------------|
| 734      |           | C32H28N6O7  | 608.62 | 9.656 99%                | 630.6                     |
| 735      |           | C28H27N5O9S | 609.62 | 10.887 92%               | 632.1                     |

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Example 35























Compounds **736-767** were prepared by methods similar to the methods used to prepare compounds **619-635** (see, Example 13). Physical data for compounds

**736-767** is listed in Table 30.

Table 30

| Compound | R <sup>4</sup> | R <sup>3</sup> |
|----------|----------------|----------------|
| 736      |                |                |
| 737      |                |                |
| 738      |                |                |
| 739      |                |                |
| 740      |                |                |
| 741      |                |                |























- 750 -

| Compound | R <sup>4</sup>  | R <sup>3</sup>  |
|----------|---|---|
| 742      |    |    |
| 743      |    |    |
| 744      |    |    |
| 745      |    |    |
| 746      |    |    |
| 747      |    |    |
| 748      |    |    |
| 749      |    |    |
| 750      |   |   |
| 751      |  |  |
| 752      |  |  |

5

10









- 751 -

| Compound | R <sup>4</sup>  | R <sup>3</sup>  |
|----------|---|---|
| 753      |    |    |
| 754      |    |    |
| 755      |    |    |
| 756      |    |    |
| 757      |    |    |
| 758      |    |    |
| 759      |    |    |
| 760      |    |    |
| 761      |    |    |
| 762      |  |  |
| 763      |  |  |

5

10

- 752 -

| Compound | R <sup>4</sup>  | R <sup>3</sup>  |
|----------|---|---|
| 764      |  |  |
| 765      |  |  |
| 766      |  |  |
| 767      |  |  |

5           The data of the examples above demonstrate that compounds according to this invention display inhibitory activity towards IL-1 $\beta$  Converting Enzyme.

          Insofar as the compounds of this invention are able to inhibit ICE in vitro and furthermore, may be  
 10 delivered orally to mammals, they are of evident clinical utility for the treatment of IL-1-, apoptosis-, IGIF-, and IFN- $\gamma$  mediated diseases. These tests are predictive of the compounds ability to inhibit ICE in vivo.

15           While we have described a number of embodiments of this invention, it is apparent that our basic constructions may be altered to provide other embodiments which utilize the products and processes of this invention. Therefore, it will be appreciated that the scope  
 20 of this invention is to be defined by the appended claims, rather than by the specific embodiments which have been presented by way of example.

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## CLAIMS

We claim:

1. A compound represented by the formula:



wherein:

10  $\text{X}_1$  is -CH; $g$  is 0 or 1;

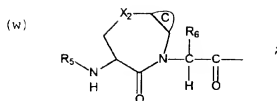
each J is independently selected from the group consisting of -H, -OH, and -F, provided that when a first and second J are bound to a C and said first J is  
 15 -OH, said second J is -H;

 $m$  is 0, 1, or 2;

T is -OH, -CO-CO<sub>2</sub>H, -CO<sub>2</sub>H, or any bioisosteric replacement for -CO<sub>2</sub>H;

$\text{R}_1$  is selected from the group consisting of the  
 20 following formulae, in which any ring may optionally be singly or multiply substituted at any carbon by  $\text{Q}_1$ , at any nitrogen by  $\text{R}_5$ , or at any atom by =O, -OH, -CO<sub>2</sub>H, or halogen; and any saturated ring may optionally be unsaturated at one or two bonds;

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wherein each ring C is independently chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

R<sub>3</sub> is:

-CN,

-CH=CH-R<sub>9</sub>,

10 -CH=N-O-R<sub>9</sub>,

-(CH<sub>2</sub>)<sub>1-3</sub>-T<sub>1</sub>-R<sub>9</sub>,

-CJ<sub>2</sub>-R<sub>9</sub>,

-CO-R<sub>13</sub>, or

15 -CO-CO-N  
/R<sub>5</sub>  
\R<sub>10</sub>;

each R<sub>4</sub> is independently selected from the group consisting of:

-H,

20 -Ar<sub>1</sub>,

-R<sub>9</sub>,

-T<sub>1</sub>-R<sub>9</sub>, and

-(CH<sub>2</sub>)<sub>1,2,3</sub>-T<sub>1</sub>-R<sub>9</sub>;

each T<sub>1</sub> is independently selected from the group consisting of:

CH=CH-,

-O-,



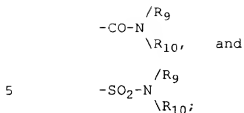
- 755 -

- S-,  
 -SO-,  
 -SO<sub>2</sub>-,  
 -NR<sub>10</sub>-,  
 5    -NR<sub>10</sub>-CO-,  
       -CO-,  
       -O-CO-,  
       -CO-O-,  
       -CO-NR<sub>10</sub>-,  
 10    -O-CO-NR<sub>10</sub>-,  
       -NR<sub>10</sub>-CO-O-,  
       -NR<sub>10</sub>-CO-NR<sub>10</sub>-,  
       -SO<sub>2</sub>-NR<sub>10</sub>-,  
       -NR<sub>10</sub>-SO<sub>2</sub>-,        and  
 15    -NR<sub>10</sub>-SO<sub>2</sub>-NR<sub>10</sub>-;

each R<sub>5</sub> is independently selected from the group consisting of:

- H,  
 -Ar<sub>1</sub>,  
 20    -CO-Ar<sub>1</sub>,  
       -SO<sub>2</sub>-Ar<sub>1</sub>,  
       -CO-NH<sub>2</sub>,  
       -SO<sub>2</sub>-NH<sub>2</sub>,  
       -R<sub>9</sub>,  
 25    -CO-R<sub>9</sub>,  
       -CO-O-R<sub>9</sub>,  
       -SO<sub>2</sub>-R<sub>9</sub>,  
       /Ar<sub>1</sub>  
       -CO-N  
 30        \R<sub>10</sub>,  
       /Ar<sub>1</sub>  
       -SO<sub>2</sub>-N  
       \R<sub>10</sub>,

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$R_6$  is:  
 -H  
 -Ar<sub>1</sub>,  
 10 -R<sub>9</sub>,  
 -(CH<sub>2</sub>)<sub>1,2,3</sub>-T<sub>1</sub>-R<sub>9</sub>, or  
 an  $\alpha$ -amino acid side chain residue;

each R<sub>9</sub> is a C<sub>1-6</sub> straight or branched alkyl group  
 optionally singly or multiply substituted with -OH, -F,  
 15 or =O and optionally substituted with one or two Ar<sub>1</sub>  
 groups;

each R<sub>10</sub> is independently selected from the group  
 consisting of -H or a C<sub>1-6</sub> straight or branched alkyl  
 group;

20 each R<sub>13</sub> is independently selected from the group  
 consisting of -Ar<sub>2</sub>, -R<sub>4</sub> and -N-OH  
 $\quad \quad \quad \backslash$   
 $\quad \quad \quad R_5$ ;

each Ar<sub>1</sub> is a cyclic group independently selected  
 25 from the set consisting of an aryl group which contains  
 6, 10, 12, or 14 carbon atoms and between 1 and 3  
 rings, a cycloalkyl group which contains between 3 and  
 15 carbon atoms and between 1 and 3 rings, said  
 cycloalkyl group being optionally benzofused, and a  
 30 heterocycle group containing between 5 and 15 ring

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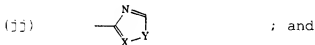
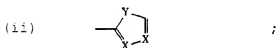
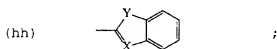
atoms and between 1 and 3 rings, said heterocycle group containing at least one heteroatom group selected from -O-, -S-, -SO-, -SO<sub>2</sub>-, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds,

5 said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted with -NH<sub>2</sub>, -CO<sub>2</sub>H, -Cl, -F, -Br, -I, -NO<sub>2</sub>, -CN,

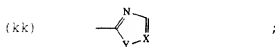
10 =O, -OH, -perfluoro C<sub>1-3</sub> alkyl,  $\begin{array}{c} \diagup \quad \diagdown \\ \text{O} \quad \quad \text{O} \\ \diagdown \quad \diagup \\ \text{CH}_2 \end{array}$ , or -Q<sub>1</sub>;

each Ar<sub>2</sub> is independently selected from the

15 following group, in which any ring may optionally be singly or multiply substituted by -Q<sub>1</sub> and -Q<sub>2</sub>:



20



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each  $Q_1$  is independently selected from the group consisting of:

-Ar,

$$-\text{O}-\text{Ar}_1$$
5  $-R_{g'}$ 
$$-T_1 - R_9, \quad \text{and}$$
$$-(\text{CH}_2)_{1,2,3}-\text{T}_1-\text{R}_9;$$

each  $Q_2$  is independently selected from the group consisting of  $-OH$ ,  $-NH_2$ ,  $-CO_2H$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-I$ ,

$-\text{NO}_2$ ,  $-\text{CN}$ ,  $-\text{CF}_3$ , and



15

provided that when  $-Ar_1$  is substituted with a  $Q_1$  group which comprises one or more additional  $-Ar_1$  groups, said additional  $-Ar_1$  groups are not substituted with  $Q_1$ ;

20        each X is independently selected from the group  
consisting of =N-, and =CH-;

each  $X_2$  is independently selected from the group consisting of  $-O-$ ,  $-\text{CH}_2-$ ,  $-\text{NH}-$ ,  $-\text{S}-$ ,  $-\text{SO}-$ , and  $-\text{SO}_2-$ ;

each Y is independently selected from the group  
25 consisting of -O-, -S-, and -NH;

provided that when

q is 0.

J 15 -H.

m 15 1.

30 T 1S -CO<sub>2</sub>H,

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 $X_2$  is O, $R_5$  is benzyloxycarbonyl, and  
ring C is benzo,then  $R_3$  cannot be  $-\text{CO}-R_{13}$  when:5  $R_{13}$  is  $-\text{CH}_2-\text{O}-\text{Ar}_1$  and $\text{Ar}_1$  is 1-phenyl-3-trifluoromethyl-  
pyrazole-5-yl wherein the phenyl is optionally  
substituted with a chlorine atom;

or when

10  $R_{13}$  is  $-\text{CH}_2-\text{O}-\text{CO}-\text{Ar}_1$ , wherein $\text{Ar}_1$  is 2,6-dichlorophenyl.2. The compound according to claim 1,  
wherein: $X_1$  is  $-\text{CH}$ ;

15

 $g$  is O; $J$  is  $-\text{H}$ ; $m$  is 0 or 1 and  $T$  is  $-\text{CO}-\text{CO}_2\text{H}$ , or any bioisosteric  
replacement for  $-\text{CO}_2\text{H}$ , or20  $m$  is 1 and  $T$  is  $-\text{CO}_2\text{H}$ ;ring C is benzo optionally substituted with  
 $-\text{C}_{1-3}$  alkyl,  $-\text{O}-\text{C}_{1-3}$  alkyl,  $-\text{Cl}$ ,  $-\text{F}$  or  $-\text{CF}_3$ ; $R_5$  is:25  $-\text{CO}-\text{Ar}_1$   
 $-\text{SO}_2-\text{Ar}_1$ ,  
 $-\text{CO}-\text{NH}_2$ ,  
 $-\text{CO}-\text{NH}-\text{Ar}_1$   
 $-\text{CO}-R_g$ ,

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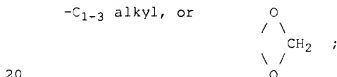
-CO-O-R<sub>9</sub>,  
 -SO<sub>2</sub>-R<sub>9</sub>, or  
 -CO-NH-R<sub>9</sub>,

5           R<sub>7</sub> is -H and R<sub>6</sub> is: -H,  
               -R<sub>9</sub>, or  
               -Ar<sub>1</sub>;

R<sub>9</sub> is a C<sub>1-6</sub> straight or branched alkyl group optionally substituted with =O and optionally substituted with -Ar<sub>1</sub>;

10           R<sub>10</sub> is H or a -C<sub>1-3</sub> straight or branched alkyl group;

              Ar<sub>1</sub> is phenyl, naphthyl, pyridyl, benzothiazolyl, thienyl, benzothienyl, benzoxazolyl, 2-indanyl, or indolyl optionally substituted with -O-C<sub>1-3</sub> alkyl, -NH-C<sub>1-3</sub> alkyl, -N-(C<sub>1-3</sub> alkyl)<sub>2</sub>, -Cl, -F, -CF<sub>3</sub>,  
 15           -C<sub>1-3</sub> alkyl, or



              Q<sub>1</sub> is R<sub>9</sub> or -(CH<sub>2</sub>)<sub>0,1,2</sub>-T<sub>1</sub>-(CH<sub>2</sub>)<sub>0,1,2</sub>-Ar<sub>1</sub>, wherein T<sub>1</sub> is -O- or -S-;

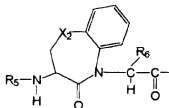
              each X is independently selected from the group consisting of =N-, and =CH-;

25           each X<sub>2</sub> is independently selected from the group consisting of -O-, -CH<sub>2</sub>-, -NH-, -S-, -SO-, and -SO<sub>2</sub>-.

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3. The compound according to claims 1 or 2,  
wherein the  $R_1$  group is:

(w1)



; wherein

5  $X_2$  is:

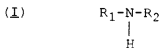
-O- ,  
-S- ,  
-SO<sub>2</sub>-, or  
-NH-;

10

optionally substituted with  $R_5$  or  $Q_1$  at  $X_2$  when  $X_2$   
is -NH-; and

ring C is benzo substituted with -C<sub>1-3</sub> alkyl,  
-O-C<sub>1-3</sub> alkyl, -Cl, -F or -CF<sub>3</sub>.

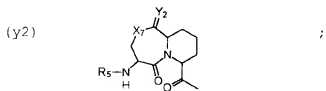
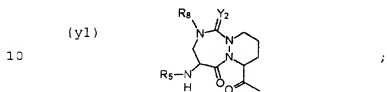
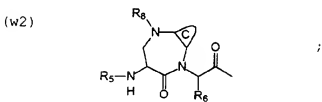
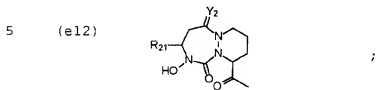
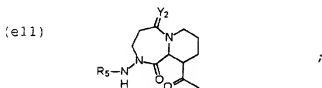
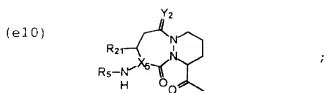
15 4. A compound represented by the formula:



wherein:

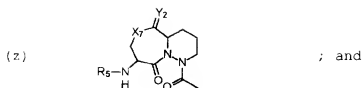
20  $R_1$  is selected from the group consisting of the  
following formulae:

- 762 -



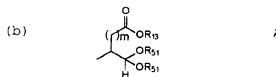
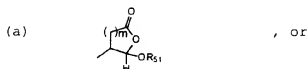


- 763 -



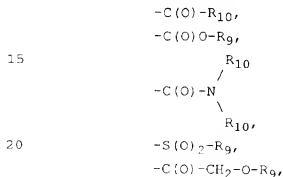
ring C is chosen from the group consisting of  
benzo, pyrido, thieno, pyrrolo, furano, thiazolo,  
5 isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo,  
cyclopentyl, and cyclohexyl;

R<sub>2</sub> is:



10 m is 1 or 2;

R<sub>5</sub> is selected from the group consisting of:



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-C(O)C(O)-R<sub>10</sub>,  
 -R<sub>9</sub>,  
 -H, and  
 -C(O)C(O)-OR<sub>10</sub>;

5           X<sub>5</sub> is -CH- or -N-;  
               |               |

Y<sub>2</sub> is H<sub>2</sub> or O;

X<sub>7</sub> is -N(R<sub>8</sub>)- or -O-;

10

R<sub>6</sub> is selected from the group consisting of -H and  
 -CH<sub>3</sub>;

R<sub>8</sub> is selected from the group consisting of:

15

-C(O)-R<sub>10</sub>,  
 -C(O)O-R<sub>9</sub>,  
 -C(O)-N(H)-R<sub>10</sub>,  
 -S(O)<sub>2</sub>-R<sub>9</sub>,  
 -S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
 20       -C(O)-CH<sub>2</sub>-OR<sub>10</sub>,  
        -C(O)C(O)-R<sub>10</sub>;  
        -C(O)-CH<sub>2</sub>N(R<sub>10</sub>)(R<sub>10</sub>),  
        -C(O)-CH<sub>2</sub>C(O)-O-R<sub>9</sub>,  
        -C(O)-CH<sub>2</sub>C(O)-R<sub>9</sub>,  
 25       -H, and  
        -C(O)-C(O)-OR<sub>10</sub>;

each R<sub>9</sub> is independently selected from the group  
 consisting of -Ar<sub>3</sub> and a -C<sub>1-6</sub> straight or branched  
 alkyl group optionally substituted with -Ar<sub>3</sub>, wherein  
 30   the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

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each R<sub>10</sub> is independently selected from the group consisting of -H, -Ar<sub>3</sub>, a -C<sub>3-6</sub> cycloalkyl group, and a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with -Ar<sub>3</sub>, wherein the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

R<sub>13</sub> is selected from the group consisting of H, Ar<sub>3</sub>, and a C<sub>1-6</sub> straight or branched alkyl group optionally substituted with -Ar<sub>3</sub>, -CONH<sub>2</sub>, -OR<sub>5</sub>, -OH, -OR<sub>9</sub>, or -CO<sub>2</sub>H;

each R<sub>51</sub> is independently selected from the group consisting of R<sub>9</sub>, -C(O)-R<sub>9</sub>, -C(O)-N(H)-R<sub>9</sub>, or each R<sub>51</sub> taken together forms a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-;

each R<sub>21</sub> is independently selected from the group consisting of -H or a -C<sub>1-6</sub> straight or branched alkyl group;

each Ar<sub>3</sub> is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

- 766 -

each  $Q_1$  is independently selected from the group consisting of  $-\text{NH}_2$ ,  $-\text{CO}_2\text{H}$ ,  $-\text{Cl}$ ,  $-\text{F}$ ,  $-\text{Br}$ ,  $-\text{I}$ ,  $-\text{NO}_2$ ,  $-\text{CN}$ ,  $=\text{O}$ ,  $-\text{OH}$ ,  $-\text{perfluoro C}_{1-3}$  alkyl,  $\text{R}_5$ ,  $-\text{OR}_5$ ,  $-\text{NHR}_5$ ,  $-\text{OR}_9$ ,  $-\text{NHR}_9$ ,  $-\text{R}_9$ ,  $-\text{C}(\text{O})-\text{R}_{10}$ , and



10 provided that when  $-\text{Ar}_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-\text{Ar}_3$  groups, said additional  $-\text{Ar}_3$  groups are not substituted with another  $-\text{Ar}_3$ .

15 5. The compound according to claim 4, wherein  $\text{R}_5$  is selected from the group consisting of:  
 $-\text{C}(\text{O})-\text{R}_{10}$ ,  
 $-\text{C}(\text{O})\text{O}-\text{R}_9$ , and  
 $-\text{C}(\text{O})-\text{NH}-\text{R}_{10}$ .

20 6. The compound according to claim 4, wherein  $\text{R}_5$  is selected from the group consisting of:  
 $-\text{S}(\text{O})_2-\text{R}_9$ ,  
 $-\text{S}(\text{O})_2-\text{NH}-\text{R}_{10}$ ,  
 $-\text{C}(\text{O})-\text{C}(\text{O})-\text{R}_{10}$ ,  
25  $-\text{R}_9$ , and  
 $-\text{C}(\text{O})-\text{C}(\text{O})-\text{OR}_{10}$ .

7. The compound according to claims 5 or 6, wherein:

m is 1;

30

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$R_{13}$  is H or a  $C_{1-4}$  straight or branched alkyl group optionally substituted with  $-Ar_3$ ,  $-OH$ ,  $-OR_9$ ,  $-CO_2H$ , wherein the  $R_9$  is a  $C_{1-4}$  branched or straight chain alkyl group; wherein  $Ar_3$  is morpholinyl or phenyl,  
 5 wherein the phenyl is optionally substituted with  $Q_1$ ;

$R_{21}$  is  $-H$  or  $-CH_3$ ;

$R_{51}$  is a  $C_{1-6}$  straight or branched alkyl group optionally substituted with  $-Ar_3$ , wherein  $Ar_3$  is phenyl, optionally substituted by  $-Q_1$ ;

10 each  $Ar_3$  cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl,  
 15 benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

each  $Q_1$  is independently selected from the group consisting of  $-NH_2$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-OH$ ,  $-R_5$ ,  $-NH-R_5$   
 20 wherein  $R_5$  is  $-C(O)-R_{10}$  or  $-S(O)_2-R_9$ ,  $-OR_5$  wherein  $R_5$  is  $-C(O)-R_{10}$ ,  $-OR_9$ ,  $-NHR_9$ , and



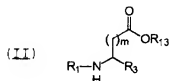
wherein each  $R_9$  and  $R_{10}$  are independently a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $-Ar_3$  wherein  $Ar_3$  is phenyl;

30

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provided that when  $-\text{Ar}_3$  is substituted with a  $\text{Q}_1$  group which comprises one or more additional  $-\text{Ar}_3$  groups, said additional  $-\text{Ar}_3$  groups are not substituted with another  $-\text{Ar}_3$ .

5 8. A compound represented by the formula:

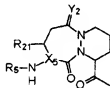


wherein:

m is 1 or 2;

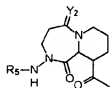
10  $\text{R}_1$  is selected from the group consisting of the following formulae:

(e10)



, wherein  $\text{X}_5$  is N;

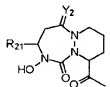
(e11)



15

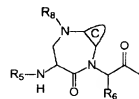
;

(e12)



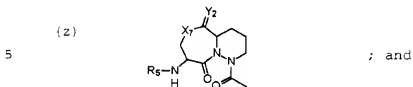
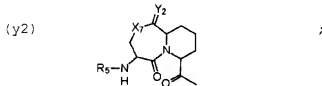
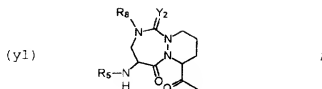
;

(w2)



;

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ring C is chosen from the group consisting of  
benzo, pyrido, thieno, pyrrolo, furano, thiazolo,  
isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo,  
10 cyclopentyl, and cyclohexyl;

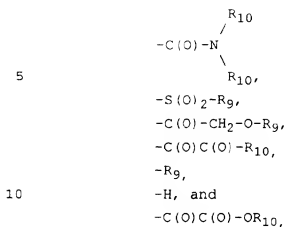
R<sub>3</sub> is selected from the group consisting of:

- CN,
- C(O)-H,
- C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>,
- 15 -C(O)-CH<sub>2</sub>-F,
- C=N-O-R<sub>9</sub>, and
- CO-Ar<sub>2</sub>;

R<sub>5</sub> is selected from the group consisting of:

- C(O)-R<sub>10</sub>,
- 20 -C(O)O-R<sub>9</sub>,

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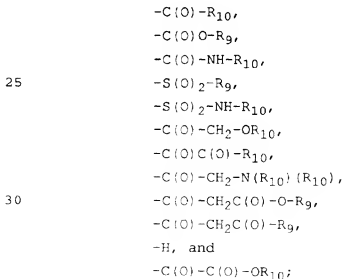
$\text{Y}_2$  is  $\text{H}_2$  or  $\text{O}$ ;

$\text{X}_7$  is  $-\text{N}(\text{R}_8)-$  or  $-\text{O}-$ ;

15 each  $\text{T}_1$  is independently selected from the group consisting of  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{S}(\text{O})-$ , and  $-\text{S}(\text{O})_2-$ ;

$\text{R}_6$  is selected from the group consisting of  $-\text{H}$  and  $-\text{CH}_3$ ;

20  $\text{R}_8$  is selected from the group consisting of:





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each  $R_9$  is independently selected from the group consisting of  $-Ar_3$  and a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $-Ar_3$ , wherein the  $-C_{1-6}$  alkyl group is optionally unsaturated;

5        each  $R_{10}$  is independently selected from the group consisting of  $-H$ ,  $-Ar_3$ , a  $-C_{3-6}$  cycloalkyl group, and a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $-Ar_3$ , wherein the  $-C_{1-6}$  alkyl group is optionally unsaturated;

10        each  $R_{11}$  is independently selected from the group consisting of:

$-Ar_4$ ,  
 $-(CH_2)_{1-3}-Ar_4$ ,  
 $-H$ , and

15         $-C(O)-Ar_4$ ;

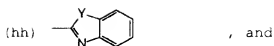
$R_{13}$  is selected from the group consisting of  $H$ ,  $Ar_3$ , and a  $C_{1-6}$  straight or branched alkyl group optionally substituted with  $-Ar_3$ ,  $-CONH_2$ ,  $-OR_5$ ,  $-OH$ ,  $-OR_9$ , or  $-CO_2H$ ;

20         $OR_{13}$  is optionally  $-N(H)-OH$ ;

each  $R_{21}$  is independently selected from the group consisting of  $-H$  or a  $-C_{1-6}$  straight or branched alkyl group;

25         $Ar_2$  is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by  $-Q_1$  or phenyl, optionally substituted by  $Q_1$ :

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wherein each Y is independently selected from the  
5 group consisting of O and S;

each Ar<sub>3</sub> is a cyclic group independently selected  
from the set consisting of an aryl group which contains  
6, 10, 12, or 14 carbon atoms and between 1 and 3 rings  
and an aromatic heterocycle group containing between 5  
10 and 15 ring atoms and between 1 and 3 rings, said  
heterocyclic group containing at least one heteroatom  
group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, and -NH-,  
-N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally  
containing one or more double bonds, said heterocycle  
15 group optionally comprising one or more aromatic rings,  
and said cyclic group optionally being singly or  
multiply substituted by -Q<sub>1</sub>;

each Ar<sub>4</sub> is a cyclic group independently selected  
from the set consisting of an aryl group which contains  
20 6, 10, 12, or 14 carbon atoms and between 1 and 3  
rings, and a heterocycle group containing between 5 and  
15 ring atoms and between 1 and 3 rings, said  
heterocyclic group containing at least one heteroatom  
group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, -NH-,  
25 -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally  
containing one or more double bonds, said heterocycle  
group optionally comprising one or more aromatic rings,  
and said cyclic group optionally being singly or  
multiply substituted by -Q<sub>1</sub>;

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each  $Q_1$  is independently selected from the group consisting of  $-NH_2$ ,  $-CO_2H$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-I$ ,  $-NO_2$ ,  $-CN$ ,  $=O$ ,  $-OH$ ,  $-perfluoro\ C_{1-3}\ alkyl$ ,  $R_5$ ,  $-OR_5$ ,  $-NHR_5$ ,  $-OR_9$ ,  $-NHR_9$ ,  $-R_9$ ,  $-C(O)-R_{10}$ , and



10

provided that when  $-Ar_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-Ar_3$  groups, said additional  $-Ar_3$  groups are not substituted with another  $-Ar_3$ .

15                    9. The compound according to claim 8, wherein  $R_1$  is (e11).

                  10. The compound according to claim 8, wherein  $R_1$  is (e12).

20                    11. The compound according to claim 8, wherein  $R_1$  is (y1).

                  12. The compound according to claim 8, wherein  $R_1$  is (y2).

                  13. The compound according to claim 8, wherein  $R_1$  is (z).

25                    14. The compound according to claim 8, wherein  $R_1$  is (w2).

                  15. The compound according to claim 14, wherein:

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m is 1;

ring C is benzo, pyrido, or thieno;

R<sub>3</sub> is selected from the group consisting of  
-C(O)-H, -C(O)-Ar<sub>2</sub>, and -C(O)CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>;

5 R<sub>5</sub> is selected from the group consisting of:

-C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is -Ar<sub>3</sub>;

-C(O)O-R<sub>9</sub>, wherein R<sub>9</sub> is -CH<sub>2</sub>-Ar<sub>3</sub>;

-C(O)C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is -Ar<sub>3</sub>;

-R<sub>9</sub>, wherein R<sub>9</sub> is a C<sub>1-2</sub> alkyl group

10 substituted with -Ar<sub>3</sub>; and

-C(O)C(O)-OR<sub>10</sub>, wherein R<sub>10</sub> is -CH<sub>2</sub>Ar<sub>3</sub>;

T<sub>1</sub> is O or S;

R<sub>6</sub> is H;

15 R<sub>8</sub> is selected from the group consisting -C(O)-R<sub>10</sub>,  
-C(O)-CH<sub>2</sub>-OR<sub>10</sub>, and -C(O)CH<sub>2</sub>-N(R<sub>10</sub>)(R<sub>10</sub>), wherein R<sub>10</sub> is  
H, CH<sub>3</sub>, or -CH<sub>2</sub>CH<sub>3</sub>;

R<sub>11</sub> is selected from the group consisting of -Ar<sub>4</sub>,  
-(CH<sub>2</sub>)<sub>1-3</sub>-Ar<sub>4</sub>, and -C(O)-Ar<sub>4</sub>;

20 R<sub>13</sub> is H or a C<sub>1-4</sub> straight or branched alkyl group  
optionally substituted with -Ar<sub>3</sub>, -OH, -OR<sub>9</sub>, -CO<sub>2</sub>H,  
wherein the R<sub>9</sub> is a C<sub>1-4</sub> branched or straight chain  
alkyl group; wherein Ar<sub>3</sub> is morpholinyl or phenyl,  
wherein the phenyl is optionally substituted with Q<sub>1</sub>;

25 Ar<sub>2</sub> is (hh);

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Y is O;

each Ar<sub>3</sub> cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, thiazolyl, benzimidazolyl, thienothienyl, thiadiazolyl, benzotriazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Ar<sub>4</sub> cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, naphthyl, pyridinyl, oxazolyl, pyrimidinyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Q<sub>1</sub> is independently selected from the group consisting of -NH<sub>2</sub>, -Cl, -F, -Br, -OH, -R<sub>9</sub>, -NH-R<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or -S(O)<sub>2</sub>-R<sub>9</sub>, -OR<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub>, -OR<sub>9</sub>, -NHR<sub>9</sub>, and



wherein each R<sub>9</sub> and R<sub>10</sub> are independently a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with -Ar<sub>3</sub> wherein Ar<sub>3</sub> is phenyl;

provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub> group which comprises one or more additional -Ar<sub>2</sub> groups, said additional -Ar<sub>3</sub> groups are not substituted with another -Ar<sub>3</sub>.

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16. The compound according to claim 8,  
wherein  $R_1$  is (e10) and  $X_5$  is N.

17. The compound according to claim 16,  
wherein  $R_3$  is CO-Ar<sub>2</sub>.

5           18. The compound according to claim 16,  
wherein  $R_3$  is -C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub> and  $R_{11}$  is -(CH<sub>2</sub>)<sub>1-3</sub>-Ar<sub>4</sub>.

19. The compound according to claim 16,  
wherein:

$R_3$  is -C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>;  
10         $T_1$  is O; and  
           $R_{11}$  is -C(O)-Ar<sub>4</sub>.

20. The compound according to claim 16,  
wherein  $R_3$  is -C(O)-H.

15       21. The compound according to claim 16,  
wherein  $R_3$  is -CO-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub> and  $R_{11}$  is -Ar<sub>4</sub>.

22. The compound according to any one of  
claims 19-21, wherein  $R_5$  is selected from the group  
consisting of:

20       -C(O)-R<sub>10</sub>,  
          -C(O)O-R<sub>9</sub>, and  
          -C(O)-NH-R<sub>10</sub>.

23. The compound according to claim 22,  
wherein:

25       m is 1;  
           $T_1$  is O or S,

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provided that when  $R_3$  is  $-C(O)-CH_2-T_1-R_{11}$ ,  $T_1$  is O;

$R_{13}$  is H or a  $C_{1-4}$  straight or branched alkyl group optionally substituted with  $-Ar_3$ ,  $-OH$ ,  $-OR_9$ ,  $-CO_2H$ ,  
5 wherein the  $R_9$  is a  $C_{1-4}$  branched or straight chain alkyl group; wherein  $Ar_3$  is morpholinyl or phenyl, wherein the phenyl is optionally substituted with  $Q_1$ ;

$R_{21}$  is  $-H$  or  $-CH_3$ ;

$Ar_2$  is (hh);

10 Y is O;

each  $Ar_3$  cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl,  
15 isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

20 each  $Ar_4$  cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

25 each  $Q_1$  is independently selected from the group consisting of  $-NH_2$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-OH$ ,  $-R_9$ ,  $-NH-R_5$  wherein  $R_5$  is  $-C(O)-R_{10}$  or  $-S(O)_2-R_9$ ,  $-OR_5$  wherein  $R_5$  is  $-C(O)-R_{10}$ ,  $-OR_9$ ,  $-NHR_9$ , and

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5

wherein each  $R_9$  and  $R_{10}$  are independently a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $-Ar_3$  wherein  $Ar_3$  is phenyl;

10 provided that when  $-Ar_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-Ar_3$  groups, said additional  $-Ar_3$  groups are not substituted with another  $-Ar_3$ .

24. The compound according to any one of  
15 claims 19-21, wherein  $R_5$  is selected from the group consisting of:

20  $-S(O)_2-R_9$ ,  
 $-S(O)_2-NH-R_{10}$ ,  
 $-C(O)-C(O)-R_{10}$ ,  
 $-R_9$ , and  
 $-C(O)-C(O)-OR_{10}$ .

25. The compound according to claim 24,  
 wherein:

25  $m$  is 1;

$T_1$  is O or S,  
 provided that when  $R_3$  is  $-C(O)-CH_2-T_1-R_{11}$ ,  $T_1$   
 is O;

30  $R_{13}$  is H or a  $C_{1-4}$  straight or branched alkyl group optionally substituted with  $-Ar_3$ ,  $-OH$ ,  $-OR_9$ ,  $-CO_2H$ ,



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wherein the  $R_9$  is a  $C_{1-4}$  branched or straight chain alkyl group; wherein  $Ar_3$  is morpholinyl or phenyl, wherein the phenyl is optionally substituted with  $Q_1$ ;

$R_{21}$  is -H or  $-CH_3$ ;

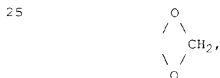
5  $Ar_2$  is (hh);

Y is O;

each  $Ar_3$  cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienethienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or  
10 multiply substituted by  $-Q_1$ ;

each  $Ar_4$  cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly  
20 or multiply substituted by  $-Q_1$ ;

each  $Q_1$  is independently selected from the group consisting of  $-NH_2$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-OH$ ,  $-R_9$ ,  $-NH-R_5$  wherein  $R_5$  is  $-C(O)-R_{10}$  or  $-S(O)_2-R_9$ ,  $-OR_5$  wherein  $R_5$  is  $-C(O)-R_{10}$ ,  $-OR_9$ ,  $-NHR_9$ , and



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wherein each  $R_9$  and  $R_{10}$  are independently a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $-Ar_3$  wherein  $Ar_3$  is phenyl;

5 provided that when  $-Ar_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-Ar_3$  groups, said additional  $-Ar_3$  groups are not substituted with another  $-Ar_3$ .

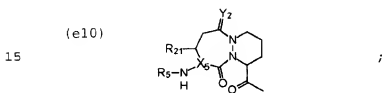
26. A compound represented by the formula:



wherein:

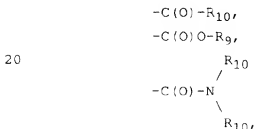
$m$  is 1 or 2;

$R_1$  is:



$R_3$  is  $-CO-Ar_2$ ;

$R_5$  is selected from the group consisting of:



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-S(O)<sub>2</sub>-R<sub>9</sub>,  
-C(O)-CH<sub>2</sub>-O-R<sub>9</sub>,  
-C(O)C(O)-R<sub>10</sub>,  
-R<sub>9</sub>,  
5        -H, and  
      -C(O)C(O)-OR<sub>10</sub>,

X<sub>5</sub> is CH;

Y<sub>2</sub> is H<sub>2</sub> or O;

10        each R<sub>9</sub> is independently selected from the group  
      consisting of -Ar<sub>3</sub> and a -C<sub>1-6</sub> straight or branched  
      alkyl group optionally substituted with -Ar<sub>3</sub>, wherein  
      the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

15        each R<sub>10</sub> is independently selected from the group  
      consisting of -H, -Ar<sub>3</sub>, a -C<sub>3-6</sub> cycloalkyl group, and a  
      -C<sub>1-6</sub> straight or branched alkyl group optionally  
      substituted with -Ar<sub>3</sub>, wherein the -C<sub>1-6</sub> alkyl group is  
      optionally unsaturated;

20        R<sub>13</sub> is selected from the group consisting of H,  
      Ar<sub>3</sub>, and a C<sub>1-6</sub> straight or branched alkyl group  
      optionally substituted with -Ar<sub>3</sub>, -CONH<sub>2</sub>, -OR<sub>5</sub>, -OH,  
      -OR<sub>9</sub>, or -CO<sub>2</sub>H;

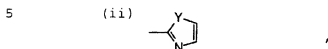
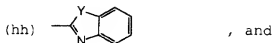
OR<sub>13</sub> is optionally -N(H)-OH;

25        each R<sub>21</sub> is independently selected from the group  
      consisting of -H or a -C<sub>1-6</sub> straight or branched alkyl  
      group;

Ar<sub>2</sub> is independently selected from the following

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group, in which any ring may optionally be singly or multiply substituted by  $-Q_1$  or phenyl, optionally substituted by  $Q_1$ :



wherein each Y is independently selected from the group consisting of O and S;

each  $Ar_3$  is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-,  $SO_2$ , =N-, and -NH-, -N( $R_5$ )-, and -N( $R_9$ )- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

each  $Ar_4$  is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-,  $SO_2$ , =N-, -NH-, -N( $R_5$ )-, and -N( $R_9$ )- said heterocycle group optionally

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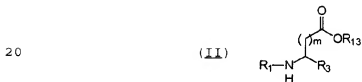
containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

5 each  $Q_1$  is independently selected from the group consisting of  $-NH_2$ ,  $-CO_2H$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-I$ ,  $-NO_2$ ,  $-CN$ ,  $=O$ ,  $-OH$ ,  $-perfluoro\ C_{1-3}\ alkyl$ ,  $R_5$ ,  $-OR_5$ ,  $-NHR_5$ ,  $-OR_9$ ,  $-NHR_9$ ,  $-R_9$ ,  $-C(O)-R_{10}$ , and



15 provided that when  $-Ar_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-Ar_3$  groups, said additional  $-Ar_3$  groups are not substituted with another  $-Ar_3$ .

27. A compound represented by the formula:



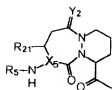
wherein:

m is 1 or 2;

$R_1$  is:

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(e10)



;

$R_3$  is  $-C(O)-CH_2-T_1-R_{11}$  and  $R_{-1}$  is  $-(CH_2)_{1-3}-Ar_4$ ;

$R_5$  is selected from the group consisting of:

5

$-C(O)-R_{10}$ ,

$-C(O)O-R_9$ ,

10

$-C(O)-N \begin{matrix} / R_{10} \\ \backslash R_{10} \end{matrix}$ ,

$-S(O)_2-R_9$ ,

$-C(O)-CH_2-O-R_9$ ,

$-C(O)C(O)-R_{10}$ ,

15

$-R_9$ ,

$-H$ , and

$-C(O)C(O)-OR_{10}$ ,

$X_5$  is  $CH$ ;

$Y_2$  is  $H_2$  or  $O$ ;

20

each  $T_1$  is independently selected from the group consisting of  $-O-$ ,  $-S-$ ,  $-S(O)-$ , and  $-S(O)_2-$ ;

25

each  $R_9$  is independently selected from the group consisting of  $-Ar_3$  and a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $-Ar_3$ , wherein the  $-C_{1-6}$  alkyl group is optionally unsaturated;

each  $R_{10}$  is independently selected from the group

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consisting of -H, -Ar<sub>3</sub>, a -C<sub>3-6</sub> cycloalkyl group, and a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with -Ar<sub>3</sub>, wherein the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

- 5           R<sub>13</sub> is selected from the group consisting of H, Ar<sub>3</sub>, and a C<sub>1-6</sub> straight or branched alkyl group optionally substituted with -Ar<sub>3</sub>, -CONH<sub>2</sub>, -OR<sub>5</sub>, -OH, -OR<sub>9</sub>, or -CO<sub>2</sub>H;

OR<sub>13</sub> is optionally -N(H)-OH;

- 10           each R<sub>21</sub> is independently selected from the group consisting of -H or a -C<sub>1-6</sub> straight or branched alkyl group;

- each Ar<sub>3</sub> is a cyclic group independently selected from the set consisting of an aryl group which contains  
15       6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, and -NH-,  
20       -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

- 25           each Ar<sub>4</sub> is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said

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heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, -NH-, -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally containing one or more double bonds, said heterocyclé  
 5 group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Q<sub>1</sub> is independently selected from the group consisting of -NH<sub>2</sub>, -CO<sub>2</sub>H, -Cl, -F, -Br, -I, -NO<sub>2</sub>, -CN,  
 10 =O, -OH, -perfluoro C<sub>1-3</sub> alkyl, -R<sub>5</sub>, -OR<sub>5</sub>, -NHR<sub>5</sub>, -OR<sub>9</sub>, -NHR<sub>9</sub>, -R<sub>9</sub>, -C(O)-R<sub>10</sub>, and



provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub> group which comprises one or more additional -Ar<sub>3</sub>  
 20 groups, said additional -Ar<sub>3</sub> groups are not substituted with another -Ar<sub>3</sub>.

28. The compound according to claims 26 or 27, wherein R<sub>5</sub> is selected from the group consisting of:

25 -C(O)-R<sub>10</sub>,  
 -C(O)O-R<sub>9</sub>, and  
 -C(O)-NH-R<sub>10</sub>.

29. The compound according to claim 28, wherein:

30 m is 1;



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T<sub>1</sub> is O or S;

R<sub>13</sub> is H or a C<sub>1-4</sub> straight or branched alkyl group optionally substituted with -Ar<sub>3</sub>, -OH, -OR<sub>9</sub>, -CO<sub>2</sub>H, wherein the R<sub>9</sub> is a C<sub>1-4</sub> branched or straight chain  
5 alkyl group; wherein Ar<sub>3</sub> is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q<sub>1</sub>;

R<sub>21</sub> is -H or -CH<sub>3</sub>;

Ar<sub>2</sub> is (hh);

Y is O;

10

each Ar<sub>3</sub> cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl,  
15 thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Ar<sub>4</sub> cyclic group is independently selected  
20 from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Q<sub>1</sub> is independently selected from the group  
25 consisting of -NH<sub>2</sub>, -Cl, -F, -Br, -OH, -R<sub>9</sub>, -NH-R<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or -S(O)<sub>2</sub>-R<sub>9</sub>, -OR<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub>, -OR<sub>9</sub>, -NHR<sub>9</sub>, and

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5

wherein each  $R_9$  and  $R_{10}$  are independently a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $-Ar_3$  wherein  $Ar_3$  is phenyl;

10 provided that when  $-Ar_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-Ar_3$  groups, said additional  $-Ar_3$  groups are not substituted with another  $-Ar_3$ .

30. The compound according to claims 26 or  
15 27, wherein  $R_5$  is selected from the group consisting of:

20  $-S(O)_2-R_9$ ,  
 $-S(O)_2-NH-R_{10}$ ,  
 $-C(O)-C(O)-R_{10}$ ,  
 $-R_9$ , and  
 $-C(O)-C(O)-OR_{10}$ .

31. The compound according to claim 30,  
wherein:

25  $m$  is 1;

$T_1$  is O or S;

$R_{13}$  is H or a  $C_{1-4}$  straight or branched alkyl group optionally substituted with  $-Ar_3$ ,  $-OH$ ,  $-OR_9$ ,  $-CO_2H$ , wherein the  $R_9$  is a  $C_{1-4}$  branched or straight chain  
30 alkyl group; wherein  $Ar_3$  is morpholinyl or phenyl,

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wherein the phenyl is optionally substituted with  $Q_1$ ;

$R_{21}$  is -H or -CH<sub>3</sub>;

$Ar_2$  is (hh);

Y is O;

5

each  $Ar_3$  cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinoliny, isoquinoliny, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

15

each  $Ar_4$  cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

20

each  $Q_1$  is independently selected from the group consisting of -NH<sub>2</sub>, -Cl, -F, -Br, -OH, -R<sub>9</sub>, -NH-R<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or -S(O)<sub>2</sub>-R<sub>9</sub>, -OR<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub>, -OR<sub>9</sub>, -NHR<sub>9</sub>, and

25



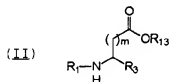
wherein each R<sub>9</sub> and R<sub>10</sub> are independently a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted

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with  $-\text{Ar}_3$  wherein  $\text{Ar}_3$  is phenyl;

provided that when  $-\text{Ar}_3$  is substituted with a  $\text{Q}_1$  group which comprises one or more additional  $-\text{Ar}_3$  groups, said additional  $-\text{Ar}_3$  groups are not substituted with another  $-\text{Ar}_3$ .

32. A compound represented by the formula:

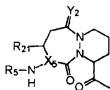


wherein:

10  $m$  is 1 or 2;

$\text{R}_1$  is:

(e10)



15  $\text{R}_3$  is  $-\text{C(O)}-\text{CH}_2-\text{T}_1-\text{R}_{11}$ ;  $\text{T}_1$  is O; and  $\text{R}_{11}$  is  $-\text{C(O)}-\text{Ar}_4$ ;

$\text{R}_5$  is selected from the group consisting of:

20  $-\text{S(O)}_2-\text{R}_9$ ,  
 $-\text{S(O)}_2-\text{NH}-\text{R}_{10}$ ,  
 $-\text{C(O)}-\text{C(O)}-\text{R}_{10}$ ,  
 $-\text{R}_9$ , and  
 $-\text{C(O)}-\text{C(O)}-\text{OR}_{10}$ ;

$\text{X}_5$  is CH;

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Y<sub>2</sub> is H<sub>2</sub> or O;

each R<sub>9</sub> is independently selected from the group consisting of -Ar<sub>3</sub> and a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with -Ar<sub>3</sub>, wherein  
5 the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

each R<sub>10</sub> is independently selected from the group consisting of -H, -Ar<sub>3</sub>, a -C<sub>3-6</sub> cycloalkyl group, and a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with -Ar<sub>3</sub>, wherein the -C<sub>1-6</sub> alkyl group is  
10 optionally unsaturated;

R<sub>13</sub> is selected from the group consisting of H, Ar<sub>3</sub>, and a C<sub>1-6</sub> straight or branched alkyl group optionally substituted with -Ar<sub>3</sub>, -CONH<sub>2</sub>, -OR<sub>5</sub>, -OH, -OR<sub>9</sub>, or -CO<sub>2</sub>H;

15 OR<sub>13</sub> is optionally -N(H)-OH;

each R<sub>21</sub> is independently selected from the group consisting of -H or a -C<sub>1-6</sub> straight or branched alkyl group;

each Ar<sub>3</sub> is a cyclic group independently selected  
20 from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom  
25 group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, and -NH-, -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings,

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and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

each  $Ar_4$  is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from  $-O-$ ,  $-S-$ ,  $-SO-$ ,  $SO_2$ ,  $=N-$ ,  $-NH-$ ,  $-N(R_5)-$ , and  $-N(R_9)-$  said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

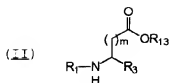
each  $Q_1$  is independently selected from the group consisting of  $-NH_2$ ,  $-CO_2H$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-I$ ,  $-NO_2$ ,  $-CN$ ,  $=O$ ,  $-OH$ ,  $-perfluoro\ C_{1-3}\ alkyl$ ,  $R_5$ ,  $-OR_5$ ,  $-NHR_5$ ,  $-OR_9$ ,  $-NHR_9$ ,  $-R_9$ ,  $-C(O)-R_{10}$ , and



provided that when  $-Ar_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-Ar_3$  groups, said additional  $-Ar_3$  groups are not substituted with another  $-Ar_3$ .

33. A compound represented by the formula:

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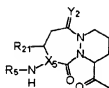


wherein:

m is 1 or 2;

 $R_1$  is:

5 (e10)



;

 $R_3$  is  $-C(O)-H$ ; $R_5$  is selected from the group consisting of:

10

 $-S(O)_2-R_9$ , $-S(O)_2-NH-R_{10}$ , $-C(O)-C(O)-R_{10}$ , $-R_9$ , and $-C(O)-C(O)-OR_{10}$ ;

15

 $X_5$  is  $CH$ ; $Y_2$  is  $H_2$  or  $O$ ;

each  $R_9$  is independently selected from the group consisting of  $-Ar_3$  and a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $-Ar_3$ , wherein  
20 the  $-C_{1-6}$  alkyl group is optionally unsaturated;

each  $R_{10}$  is independently selected from the group consisting of  $-H$ ,  $-Ar_3$ , a  $-C_{3-6}$  cycloalkyl group, and a

- 794 -

-C<sub>1-6</sub> straight or branched alkyl group optionally substituted with -Ar<sub>3</sub>, wherein the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

5           R<sub>13</sub> is selected from the group consisting of H, Ar<sub>3</sub>, and a C<sub>1-6</sub> straight or branched alkyl group optionally substituted with -Ar<sub>3</sub>, -CONH<sub>2</sub>, -OR<sub>5</sub>, -OH, -OR<sub>9</sub>, or -CO<sub>2</sub>H;

OR<sub>13</sub> is optionally -N(H)-OH;

10           each R<sub>21</sub> is independently selected from the group consisting of -H or a -C<sub>1-6</sub> straight or branched alkyl group;

15           each Ar<sub>3</sub> is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, and -NH-, -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally  
20           containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

25           each Q<sub>1</sub> is independently selected from the group consisting of -NH<sub>2</sub>, -CO<sub>2</sub>H, -Cl, -F, -Br, -I, -NO<sub>2</sub>, -CN, -C, -OH, -perfluoro C<sub>1-3</sub> alkyl, R<sub>5</sub>, -OR<sub>5</sub>, -NHR<sub>5</sub>, -OR<sub>9</sub>, -NHR<sub>9</sub>, -R<sub>9</sub>, -C(O)-R<sub>10</sub>, and



- 795 -

5



provided that when  $-\text{Ar}_3$  is substituted with a  $\text{Q}_1$  group which comprises one or more additional  $-\text{Ar}_3$  groups, said additional  $-\text{Ar}_3$  groups are not substituted with another  $-\text{Ar}_3$ .

34. The compound according to claims 32 or 33, wherein:

$m$  is 1;

15  $\text{R}_{13}$  is H or a  $\text{C}_{1-4}$  straight or branched alkyl group optionally substituted with  $-\text{Ar}_3$ ,  $-\text{OH}$ ,  $-\text{OR}_9$ ,  $-\text{CO}_2\text{H}$ , wherein the  $\text{R}_9$  is a  $\text{C}_{1-4}$  branched or straight chain alkyl group; wherein  $\text{Ar}_3$  is morpholinyl or phenyl, wherein the phenyl is optionally substituted with  $\text{Q}_1$ ;

20  $\text{R}_{21}$  is  $-\text{H}$  or  $-\text{CH}_3$ ;

each  $\text{Ar}_3$  cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, 25 isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by  $-\text{Q}_1$ ;

30 each  $\text{Ar}_4$  cyclic group is independently selected from the set consisting of phenyl, tetrazolyl,

- 796 -

pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

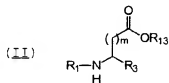
each  $Q_1$  is independently selected from the group consisting of  $-\text{NH}_2$ ,  $-\text{Cl}$ ,  $-\text{F}$ ,  $-\text{Br}$ ,  $-\text{OH}$ ,  $-\text{R}_9$ ,  $-\text{NH}-\text{R}_5$  wherein  $\text{R}_5$  is  $-\text{C}(\text{O})-\text{R}_{10}$  or  $-\text{S}(\text{O})_2-\text{R}_9$ ,  $-\text{OR}_5$  wherein  $\text{R}_5$  is  $-\text{C}(\text{O})-\text{R}_{10}$ ,  $-\text{OR}_9$ ,  $-\text{NHR}_9$ , and



wherein each  $\text{R}_9$  and  $\text{R}_{10}$  are independently a  $-\text{C}_{1-6}$  straight or branched alkyl group optionally substituted with  $-\text{Ar}_3$  wherein  $\text{Ar}_3$  is phenyl;

provided that when  $-\text{Ar}_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-\text{Ar}_3$  groups, said additional  $-\text{Ar}_3$  groups are not substituted with another  $-\text{Ar}_3$ .

35. A compound represented by the formula:

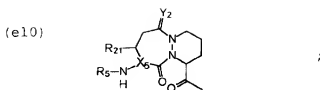


wherein:

$m$  is 1;

25  $\text{R}_1$  is:

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$R_3$  is  $-\text{CO}-\text{CH}_2-\text{T}_1-\text{R}_{11}$  and  $\text{R}_{11}$  is  $-\text{Ar}_4$ ;

$\text{R}_5$  is selected from the group consisting of:

- 5      $-\text{C}(\text{O})-\text{R}_{10}$ ,  
         $-\text{C}(\text{O})\text{O}-\text{R}_9$ , and  
         $-\text{C}(\text{O})-\text{NH}-\text{R}_{10}$ ;

$\text{X}_5$  is CH;

$\text{Y}_2$  is O;

10      $\text{T}_1$  is O or S;

each  $\text{R}_9$  is independently selected from the group consisting of  $-\text{Ar}_3$  and a  $-\text{C}_{1-6}$  straight or branched alkyl group optionally substituted with  $-\text{Ar}_3$ , wherein  
 15     the  $-\text{C}_{1-6}$  alkyl group is optionally unsaturated;

each  $\text{R}_{10}$  is independently selected from the group consisting of  $-\text{H}$ ,  $-\text{Ar}_3$ , a  $-\text{C}_{3-6}$  cycloalkyl group, and a  $-\text{C}_{1-6}$  straight or branched alkyl group optionally substituted with  $-\text{Ar}_3$ , wherein the  $-\text{C}_{1-6}$  alkyl group is  
 20     optionally unsaturated;

$\text{R}_{13}$  is H or a  $\text{C}_{1-4}$  straight or branched alkyl group optionally substituted with  $-\text{Ar}_3$ ,  $-\text{CH}$ ,  $-\text{OR}_9$ ,  $-\text{CO}_2\text{H}$ , wherein the  $\text{R}_9$  is a  $\text{C}_{1-4}$  branched or straight chain alkyl group; wherein  $\text{Ar}_3$  is morpholinyl or phenyl,

- 798 -

wherein the phenyl is optionally substituted with  $Q_1$ ;

$R_{21}$  is -H or  $-CH_3$ ;

each  $Ar_3$  cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinylnyl, isoquinolinylnyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

each  $Ar_4$  cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

each  $Q_2$  is independently selected from the group consisting of  $-NH_2$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-OH$ ,  $-R_9$ ,  $-NH-R_5$  wherein  $R_5$  is  $-C(O)-R_{10}$  or  $-S(O)_2-R_9$ ,  $-OR_5$  wherein  $R_5$  is  $-C(O)-R_{10}$ ,  $-OR_9$ ,  $-NHR_9$ , and



25 wherein each  $R_9$  and  $R_{10}$  are independently a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $-Ar_3$  wherein  $Ar_3$  is phenyl;

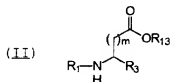
provided that when  $-Ar_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-Ar_3$

30

- 799 -

groups, said additional  $-\text{Ar}_3$  groups are not substituted with another  $-\text{Ar}_3$ .

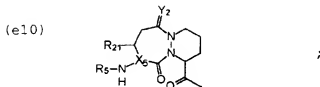
36. A compound represented by the formula:



5 wherein:

$m$  is 1;

$\text{R}_1$  is:



$\text{R}_3$  is  $-\text{CO}-\text{CH}_2-\text{T}_1-\text{R}_{11}$  and  $\text{R}_{11}$  is  $-\text{Ar}_4$ ;

$\text{R}_5$  is selected from the group consisting of:

$-\text{S}(\text{O})_2-\text{R}_9$ ,

$-\text{S}(\text{O})_2-\text{NH}-\text{R}_{10}$ ,

$-\text{C}(\text{O})-\text{C}(\text{O})-\text{R}_{10}$ ,

$-\text{R}_9$ , and

$-\text{C}(\text{O})-\text{C}(\text{O})-\text{OR}_{10}$ ;

$\text{X}_5$  is  $\text{CH}$ ;

$\text{Y}_2$  is  $\text{O}$ ;

$\text{T}_1$  is  $\text{O}$  or  $\text{S}$ ;

- 800 -

each  $R_9$  is independently selected from the group consisting of  $-Ar_3$  and a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $-Ar_3$ , wherein the  $-C_{1-6}$  alkyl group is optionally unsaturated;

- 5        each  $R_{10}$  is independently selected from the group consisting of  $-H$ ,  $-Ar_3$ , a  $-C_{3-6}$  cycloalkyl group, and a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $-Ar_3$ , wherein the  $-C_{1-6}$  alkyl group is optionally unsaturated;

- 10        $R_{13}$  is  $H$  or a  $C_{1-4}$  straight or branched alkyl group optionally substituted with  $-Ar_3$ ,  $-OH$ ,  $-OR_9$ ,  $-CO_2H$ , wherein the  $R_9$  is a  $C_{1-4}$  branched or straight chain alkyl group; wherein  $Ar_3$  is morpholinyl or phenyl, wherein the phenyl is optionally substituted with  $Q_1$ ;

- 15        $R_{21}$  is  $-H$  or  $-CH_3$ ;

- each  $Ar_3$  cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, 20        thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

- each  $Ar_4$  cyclic group is independently selected 25        from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

- 801 -

each  $Q_1$  is independently selected from the group consisting of  $-NH_2$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-OH$ ,  $-R_9$ ,  $-NH-R_5$  wherein  $R_5$  is  $-C(O)-R_{10}$  or  $-S(O)_2-R_9$ ,  $-OR_5$  wherein  $R_5$  is  $-C(O)-R_{10}$ ,  $-OR_9$ ,  $-NHR_9$ , and

5



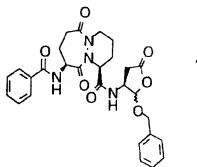
10 wherein each  $R_9$  and  $R_{10}$  are independently a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $-Ar_3$  wherein  $Ar_3$  is phenyl;

15 provided that when  $-Ar_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-Ar_3$  groups, said additional  $-Ar_3$  groups are not substituted with another  $-Ar_3$ .

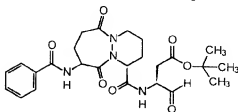
37. The compound according to claim 7 selected from the group consisting of:

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213e

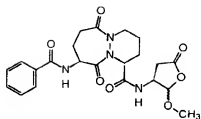


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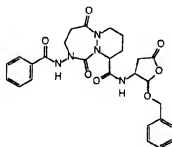
- 802 -

304a



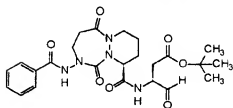
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813e



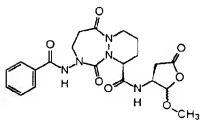
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902



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904a



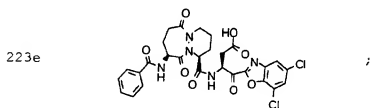
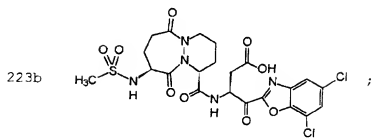
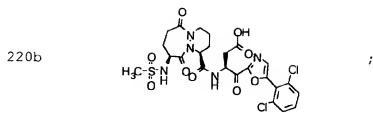
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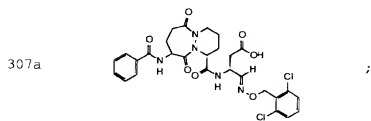
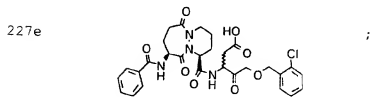
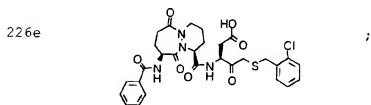
38. The compound according to claims 8 or 68, selected from the group consisting of:



- 803 -

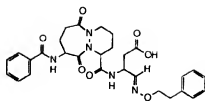


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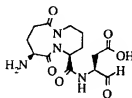
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307b



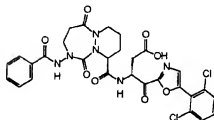
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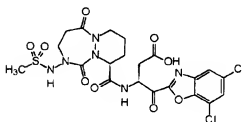
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820b



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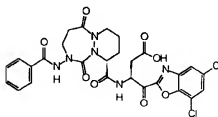
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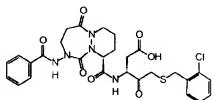
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823e



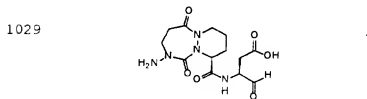
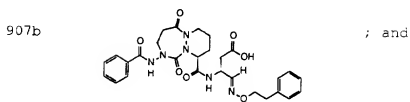
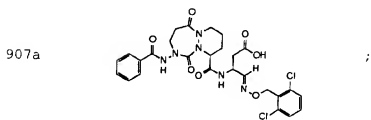
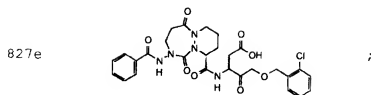
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826e

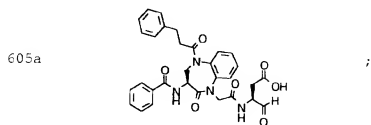


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- 805 -

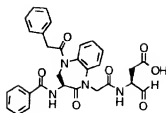


- 5                    39. The compound according to claim 15  
selected from the group consisting of:



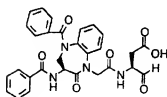
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605b



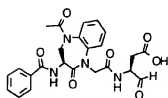
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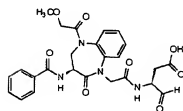
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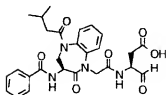
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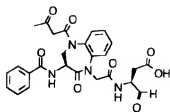
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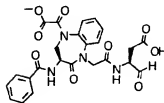
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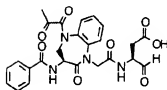
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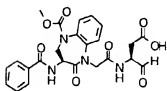
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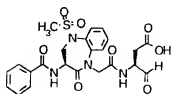
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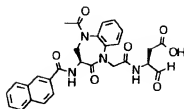
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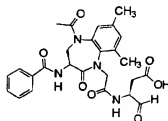
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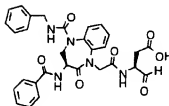
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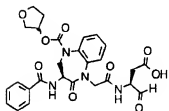
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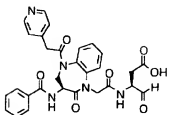
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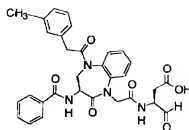
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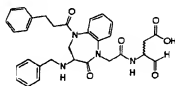
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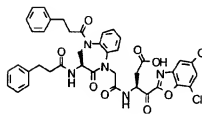
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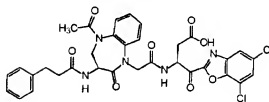
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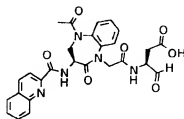
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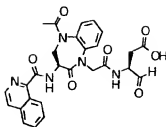
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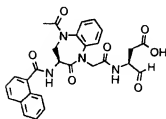
- 810 -

620

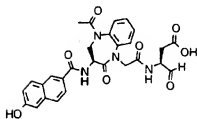


;

621

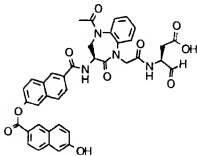
*i*

622



;

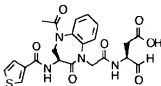
623



;

5

624

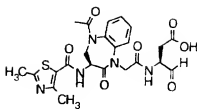


;



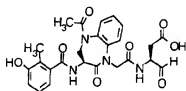
- 811 -

625



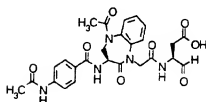
i

626



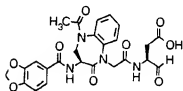
2

627



i

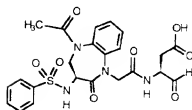
628



;

5

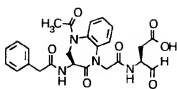
629



;

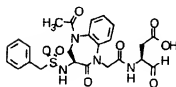
- 812 -

630



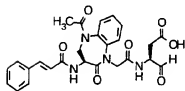
;

631



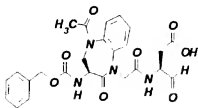
;

632



;

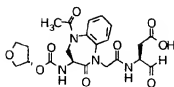
633



;

5

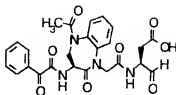
634



; and

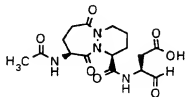
- 813 -

635



40. The compound according to claims 8 or 68, selected from the group consisting of:

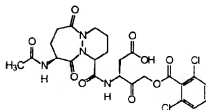
214c



;

5

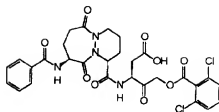
217c



;

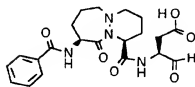
- 814 -

217e



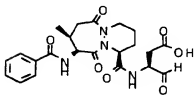
;

246



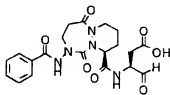
;

257



;

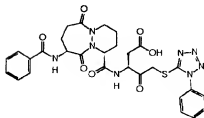
265



;

5

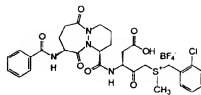
280



;

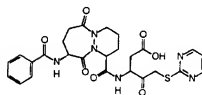
- 815 -

281



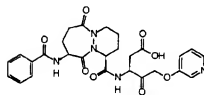
;

282



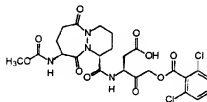
;

283



;

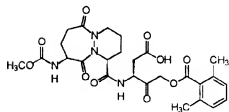
284



;

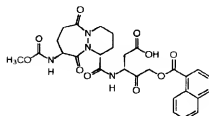
5

285



;

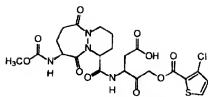
286



;

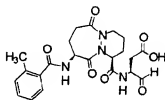
- 816 -

287



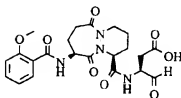
;

404



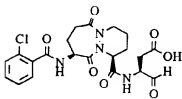
;

405



;

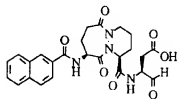
406



;

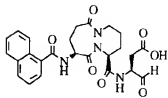
5

407



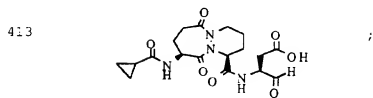
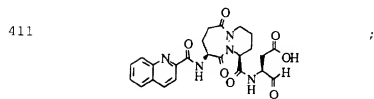
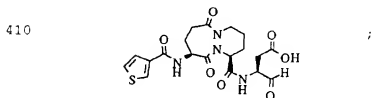
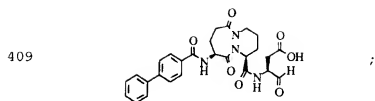
;

408

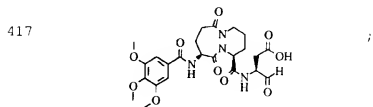
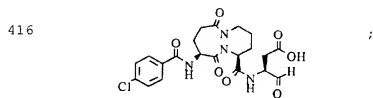


;

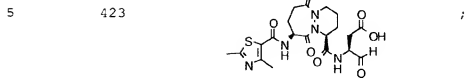
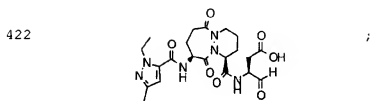
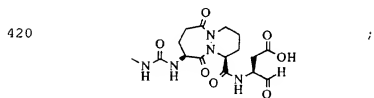
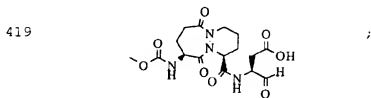
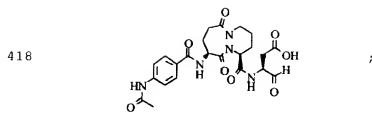
- 817 -



5



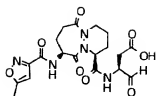
- 818 -





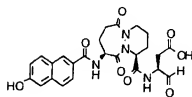
- 819 -

424



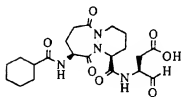
;

425



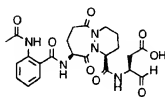
;

426



;

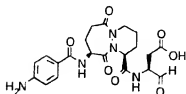
430



;

5

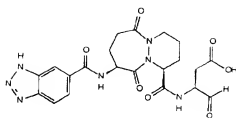
431



;

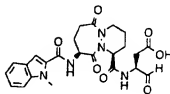
- 820 -

432



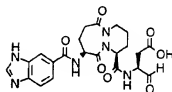
;

433



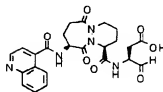
;

434



;

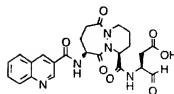
435



;

5

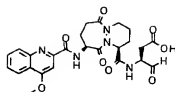
436



;

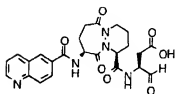
- 821 -

437



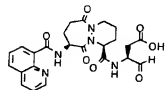
;

438



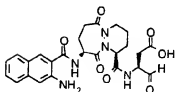
;

439



;

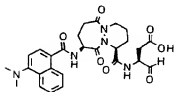
440



;

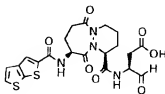
5

441



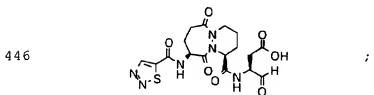
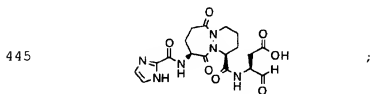
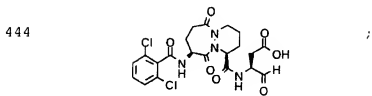
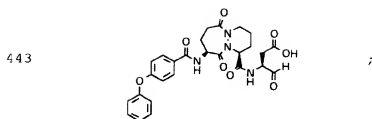
;

442

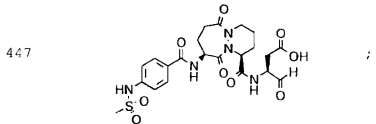


;

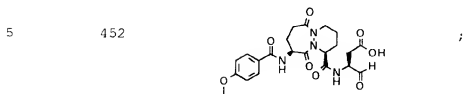
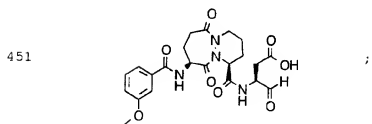
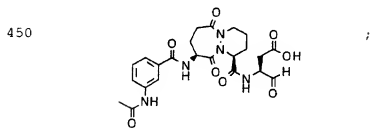
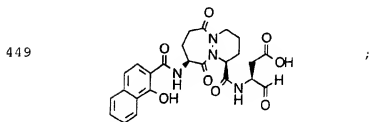
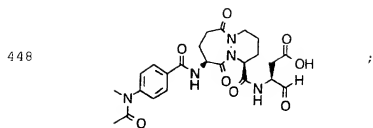
- 822 -



5

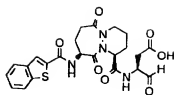


- 823 -



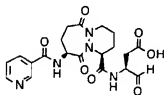
- 824 -

453



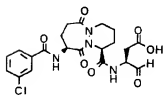
;

454



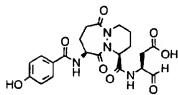
;

455



;

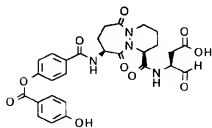
456



;

5

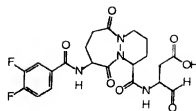
457



;

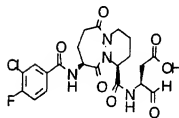
- 825 -

458



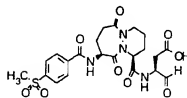
;

459



;

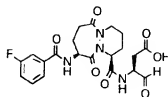
460



;

5

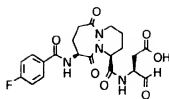
462



;

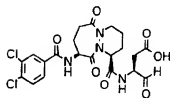
- 826 -

463



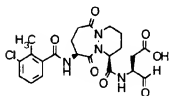
;

464



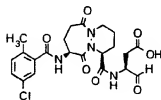
;

465



;

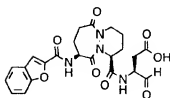
466



;

5

467

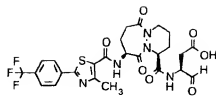


;



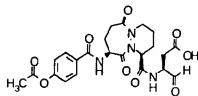
- 827 -

468



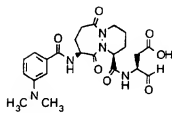
;

469



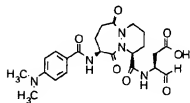
;

470



;

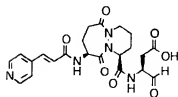
471



;

5

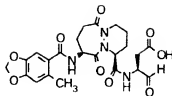
472



;

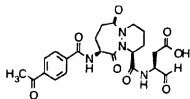
- 828 -

473



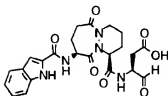
;

474



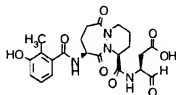
;

475



;

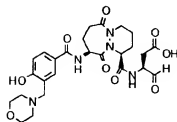
476



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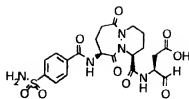
477



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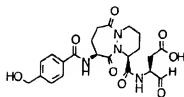
- 829 -

478



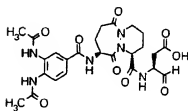
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479



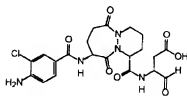
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480



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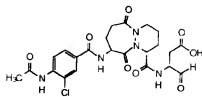
481



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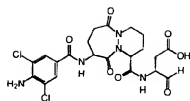
481s



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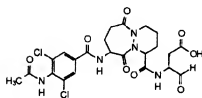
- 830 -

482



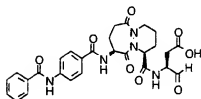
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482s



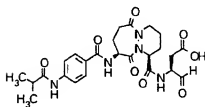
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483



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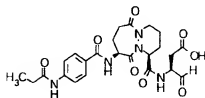
484



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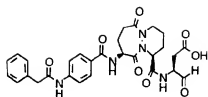
485



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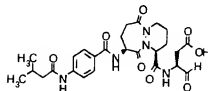
- 831 -

486



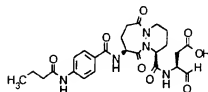
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487



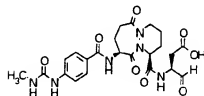
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488



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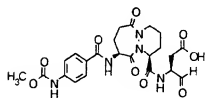
489



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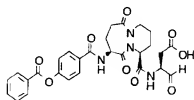
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490



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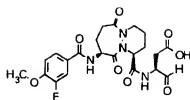
491



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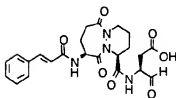
- 832 -

493



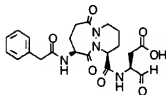
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494



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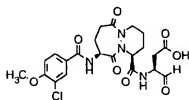
495



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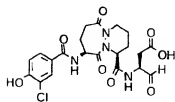
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497



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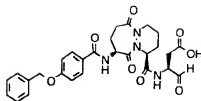
498



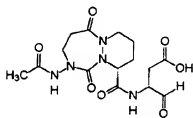
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- 833 -

499

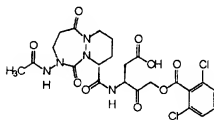
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814C



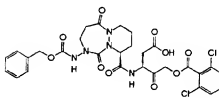
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817c



2

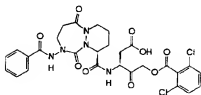
817d



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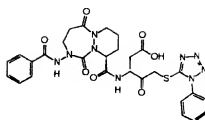
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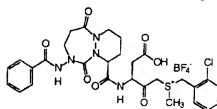
- 834 -

880



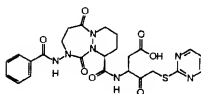
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881



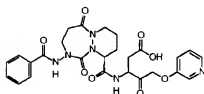
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882



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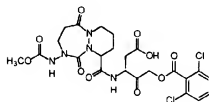
883



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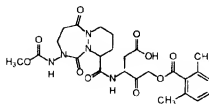
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884



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885

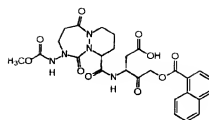


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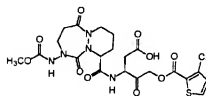
- 835 -

886



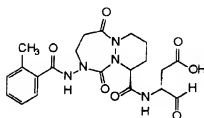
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887



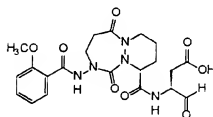
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1004



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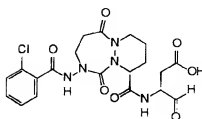
1005



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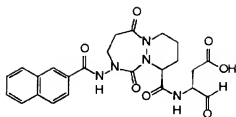
1006



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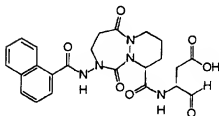
- 836 -

1007



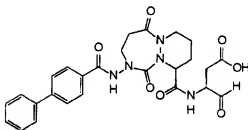
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1008



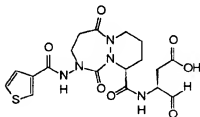
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1009



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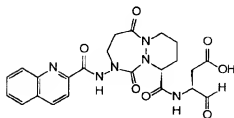
1010



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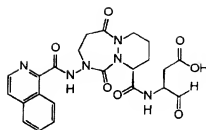
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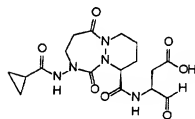
- 837 -

1012



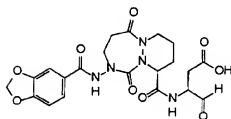
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1013



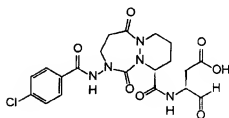
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1015



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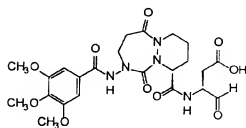
1016



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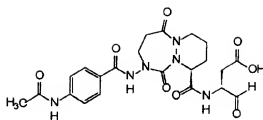
1017



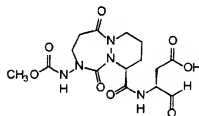
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- 838 -

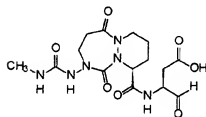
1018



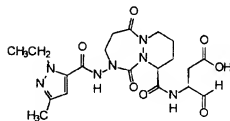
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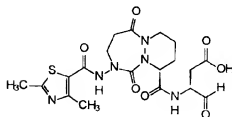


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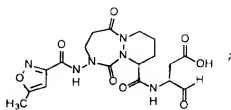
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1023

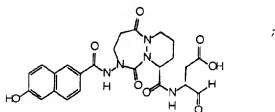


- 839 -

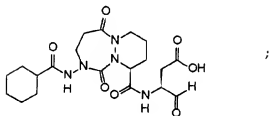
1024



1025

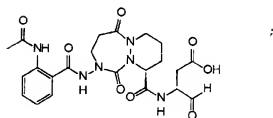


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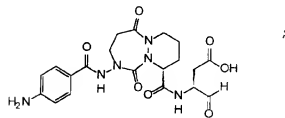


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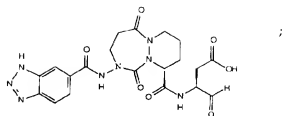


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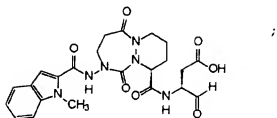


- 840 -

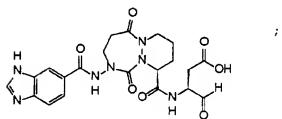
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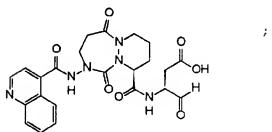
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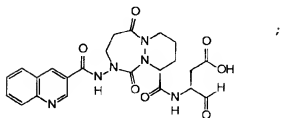


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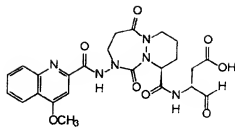
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1036



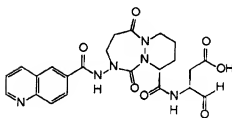
- 841 -

1037



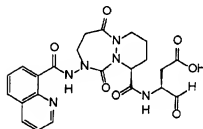
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1038



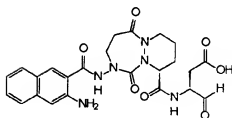
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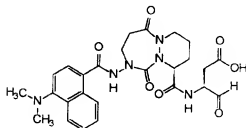
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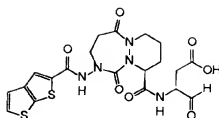
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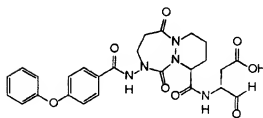
- 842 -

1042



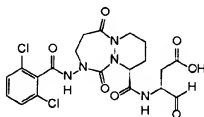
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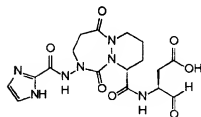
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1044



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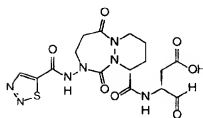
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1046

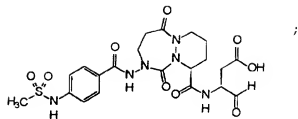


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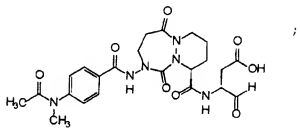


- 843 -

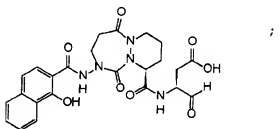
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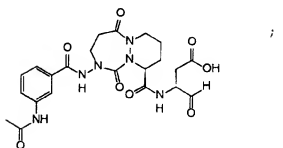
1048



1049

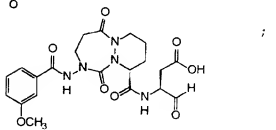


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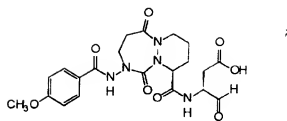
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1051

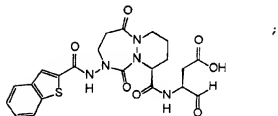


- 844 -

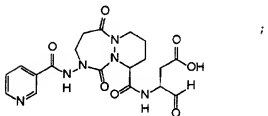
1052



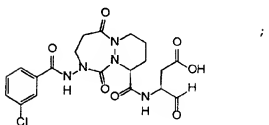
1053



1054



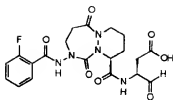
1055



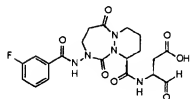


- 846 -

1061

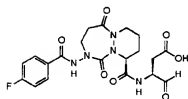
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1062



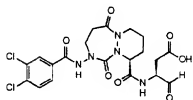
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1063



*i*

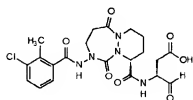
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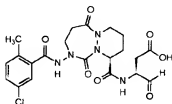
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1065



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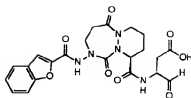
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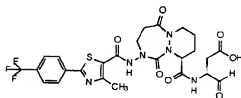
- 847 -

1067



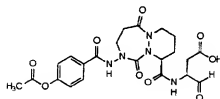
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1068



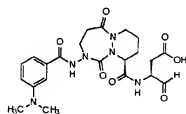
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1069



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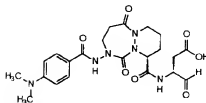
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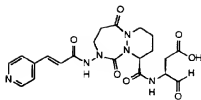
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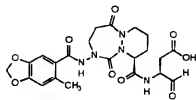
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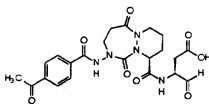
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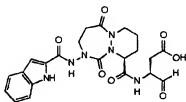
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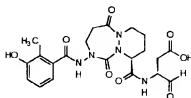
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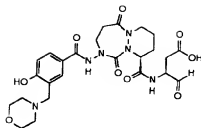
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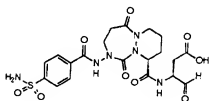
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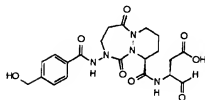
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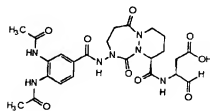
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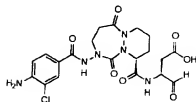
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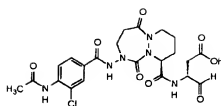
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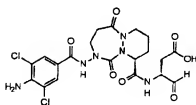
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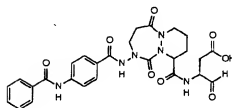
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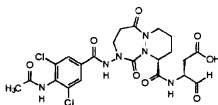
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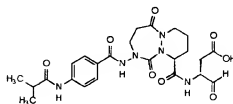
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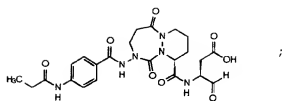


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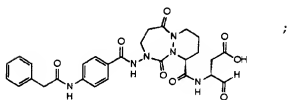


- 851 -

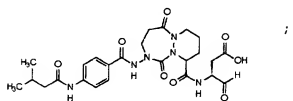
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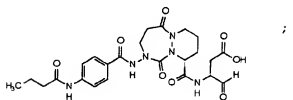
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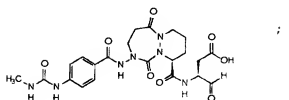


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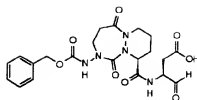
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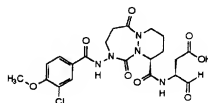
- 853 -

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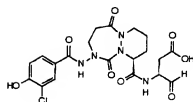
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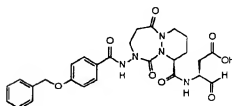
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; and

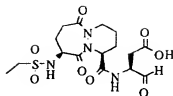
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- 5                    41. The compound according to claim 33  
selected from the group consisting of:

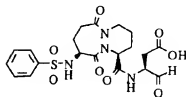
- 854 -

421



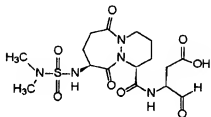
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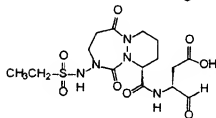
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428



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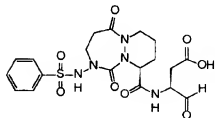
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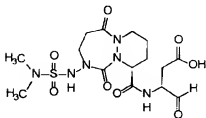
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; and

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.

42. A pharmaceutical composition comprising

- 855 -

an ICE inhibitor according to any one of claims 1-41 and 57-135 in an amount effective for treating or preventing an IL-1-mediated disease and a pharmaceutically acceptable carrier.

5                   43. A pharmaceutical composition comprising an ICE inhibitor according to any one of claims 1-41 and 57-135 in an amount effective for treating or preventing an apoptosis-mediated disease and a pharmaceutically acceptable carrier.

10                   44. The pharmaceutical composition according to claim 42, wherein the IL-1-mediated disease is an inflammatory disease selected from the group consisting of osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, and adult respiratory distress  
15                   syndrome.

                  45. The pharmaceutical composition according to claim 44, wherein the inflammatory disease is osteoarthritis or acute pancreatitis.

                  46. The pharmaceutical composition according  
20                   to claim 42, wherein the IL-1-mediated disease is an autoimmune disease selected from the group consisting of glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Grave's disease, autoimmune gastritis, insulin-  
25                   dependent diabetes mellitus (Type I), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, inflammatory bowel disease, Crohn's disease, psoriasis, and graft vs host disease.

- 856 -

47. The pharmaceutical composition according to claim 46, wherein the autoimmune disease is rheumatoid arthritis, inflammatory bowel disease, or Crohn's disease, or psoriasis.

5           48. The pharmaceutical composition according to claim 42, wherein the IL-1-mediated disease is a destructive bone disorder selected from the group consisting of osteoporosis or multiple myeloma-related bone disorder.

10           49. The pharmaceutical composition according to claim 42, wherein the IL-1-mediated disease is a proliferative disorder selected from the group consisting of acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's  
15           sarcoma, and multiple myeloma.

50. The pharmaceutical composition according to claim 42, wherein the IL-1-mediated disease is an infectious disease, selected from the group consisting of sepsis, septic shock, and Shigellosis.

20           51. The pharmaceutical composition according to claim 42, wherein the IL-1-mediated disease is a degenerative or necrotic disease, selected from the group consisting of Alzheimer's disease, Parkinson's disease, cerebral ischemia, and myocardial ischemia.

25           52. The pharmaceutical composition according to claim 51, wherein the degenerative disease is Alzheimer's disease.

53. The pharmaceutical composition according

- 857 -

to claim 43, wherein the apoptosis-mediated disease is a degenerative disease, selected from the group consisting of Alzheimer's disease, Parkinson's disease, cerebral ischemia, myocardial ischemia, spinal muscular atrophy, multiple sclerosis, AIDS-related encephalitis, HIV-related encephalitis, aging, alopecia, and neurological damage due to stroke.

54. A pharmaceutical composition for inhibiting an ICE-mediated function comprising an ICE inhibitor according to any one of claims 1-41 and 57-135 and a pharmaceutically acceptable carrier.

55. A method for treating or preventing a disease selected from the group consisting of an IL-1 mediated disease, an apoptosis mediated disease, an inflammatory disease, an autoimmune disease, a destructive bone disorder, a proliferative disorder, an infectious disease, a degenerative disease, a necrotic disease, osteoarthritis, pancreatitis, asthma, adult respiratory distress syndrome, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Grave's disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, inflammatory bowel disease, Crohn's disease, psoriasis, graft vs host disease, osteoporosis, multiple myeloma-related bone disorder, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma, sepsis, septic shock, Shigellosis, Alzheimer's disease, Parkinson's disease, cerebral ischemia, myocardial ischemia, spinal muscular

- 858 -

atrophy, multiple sclerosis, AIDS-related encephalitis, HIV-related encephalitis, aging, alopecia, and neurological damage due to stroke in a patient comprising the step of administering to said patient a pharmaceutical composition according to any one of claims 42 to 54.

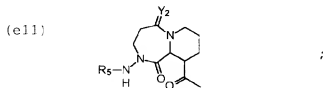
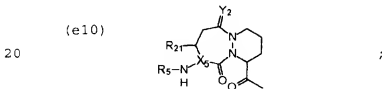
56. The method according to claim 55, wherein the disease is selected from the group consisting of osteoarthritis, acute pancreatitis, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, psoriasis, and Alzheimer's disease.

57. A compound represented by the formula:



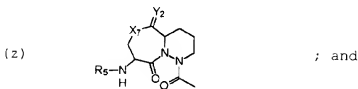
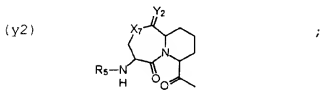
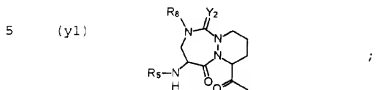
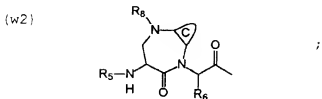
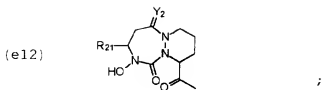
wherein:

$R_1$  is selected from the group consisting of the following formulae:





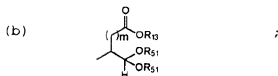
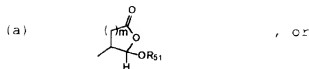
- 859 -



10 ring C is chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

R<sub>2</sub> is:

- 860 -



m is 1 or 2;

5 each R<sub>5</sub> is independently selected from the group consisting of:

- C(O)-R<sub>10</sub>,
- C(O)-O-R<sub>9</sub>,
- C(O)-N(R<sub>10</sub>)(R<sub>10</sub>)
- 10 -S(O)<sub>2</sub>-R<sub>9</sub>,
- S(O)<sub>2</sub>-NH-R<sub>10</sub>,
- C(O)-CH<sub>2</sub>-O-R<sub>9</sub>,
- C(O)C(O)-R<sub>10</sub>,
- R<sub>9</sub>,
- 15 -H,
- C(O)C(O)-OR<sub>10</sub>, and
- C(O)C(O)-N(R<sub>9</sub>)(R<sub>10</sub>);

X<sub>5</sub> is CH or N;

20 Y<sub>2</sub> is H<sub>2</sub> or O;

X<sub>7</sub> is -N(R<sub>6</sub>)- or -O-;

25 R<sub>6</sub> is selected from the group consisting of -H and -CH<sub>3</sub>;

- 861 -

R<sub>8</sub> is selected from the group consisting of:

- C(O)-R<sub>10</sub>,
- C(O)-O-R<sub>9</sub>,
- C(O)-N(H)-R<sub>10</sub>,
- 5       -S(O)<sub>2</sub>-R<sub>9</sub>,
- S(O)<sub>2</sub>-NH-R<sub>10</sub>,
- C(O)-CH<sub>2</sub>-OR<sub>10</sub>,
- C(O)C(O)-R<sub>10</sub>;
- C(O)-CH<sub>2</sub>N(R<sub>10</sub>)(R<sub>10</sub>),
- 10       -C(O)-CH<sub>2</sub>C(O)-O-R<sub>9</sub>,
- C(O)-CH<sub>2</sub>C(O)-R<sub>9</sub>,
- H, and
- C(O)-C(O)-OR<sub>10</sub>;

- each R<sub>9</sub> is independently selected from the group  
15       consisting of -Ar<sub>3</sub> and a -C<sub>1-6</sub> straight or branched  
       alkyl group optionally substituted with -Ar<sub>3</sub>, wherein  
       the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

- each R<sub>10</sub> is independently selected from the group  
consisting of -H, -Ar<sub>3</sub>, a -C<sub>3-6</sub> cycloalkyl group, and a  
20       -C<sub>1-6</sub> straight or branched alkyl group optionally  
       substituted with -Ar<sub>3</sub>, wherein the -C<sub>1-6</sub> alkyl group is  
       optionally unsaturated;

- R<sub>13</sub> is selected from the group consisting of H,  
Ar<sub>3</sub>, and a -C<sub>1-6</sub> straight or branched alkyl group  
25       optionally substituted with -Ar<sub>3</sub>, -CONH<sub>2</sub>, -OR<sub>5</sub>, -OH,  
       -OR<sub>9</sub>, or -CO<sub>2</sub>H;

- each R<sub>51</sub> is independently selected from the group  
consisting of R<sub>9</sub>, -C(O)-R<sub>9</sub>, -C(O)-N(H)-R<sub>9</sub>, or each R<sub>51</sub>  
taken together forms a saturated 4-8 member carbocyclic  
30       ring or heterocyclic ring containing -O-, -S-, or -NH-;

- 862 -

each  $R_2$  is independently selected from the group consisting of -H or a  $C_{1-6}$  straight or branched alkyl group;

5 each  $Ar_3$  is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom  
 10 group selected from -O-, -S-, -SO-,  $SO_2$ , =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted  
 15 by  $-Q_1$ ;

each  $Q_1$  is independently selected from the group consisting of  $-NH_2$ ,  $-CO_2H$ , -Cl, -F, -Br, -I,  $-NO_2$ , -CN, =O, -OH, -perfluoro  $C_{1-3}$  alkyl,  $R_5$ ,  $-OR_5$ ,  $-NHR_5$ ,  $-OR_9$ ,  
 20  $-N(R_9)(R_{10})$ ,  $-R_9$ ,  $-C(O)-R_{10}$ , and



25

provided that when  $-Ar_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-Ar_3$  groups, said additional  $-Ar_3$  groups are not substituted with another  $-Ar_3$ .

30 58. The compound according to claim 57, wherein  $R_1$  is (w2).

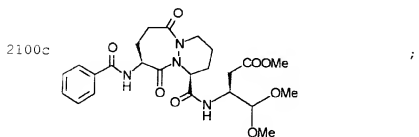
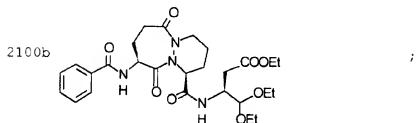
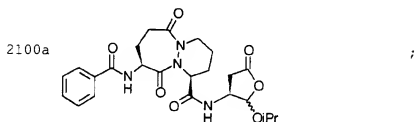
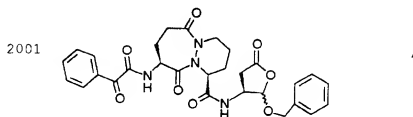
59. The compound according to claim 57,

- 863 -

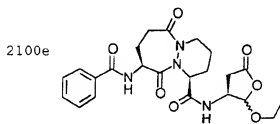
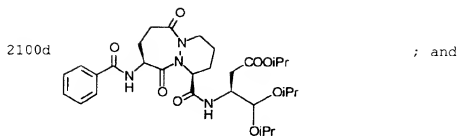
wherein  $R_1$  is (e10) and  $X_5$  is CH.

60. The compound according to claim 57,  
wherein  $R_1$  is (e10) and  $X_5$  is N.

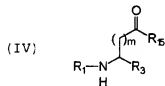
61. The compound according to claim 57,  
5 selected from the group consisting of:



- 864 -



62. A compound represented by the formula:

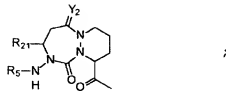


5        wherein:

$m$  is 1 or 2;

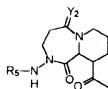
$R_1$  is selected from the group consisting of the following formulae:

10 (e10-A)



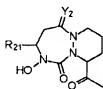
- 865 -

(e11)



;

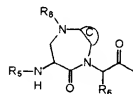
(e12)



;

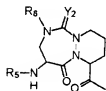
5

(w2)



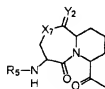
;

(y1)



;

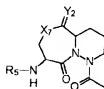
(y2)



; and

10

{z}



;

ring C is chosen from the group consisting of  
 15 benzo, pyrido, thieno, pyrrolo, furano, thiazolo,  
 isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo,

- 866 -

cyclopentyl, and cyclohexyl;

 $R_3$  is selected from the group consisting of:

- CN,
- C(O)-H,
- 5       -C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>,
- C(O)-CH<sub>2</sub>-F,
- C=N-O-R<sub>9</sub>, and
- CO-Ar<sub>2</sub>;

10       each  $R_5$  is independently selected from the group  
consisting of:

- C(O)-R<sub>10</sub>,
- C(O)O-R<sub>9</sub>,
- C(O)-N(R<sub>10</sub>)(R<sub>10</sub>)
- S(O)<sub>2</sub>-R<sub>9</sub>,
- 15       -S(O)<sub>2</sub>-NH-R<sub>10</sub>,
- C(O)-CH<sub>2</sub>-O-R<sub>9</sub>,
- C(O)C(O)-R<sub>10</sub>,
- R<sub>9</sub>,
- H,
- 20       -C(O)C(O)-OR<sub>10</sub>, and
- C(O)C(O)-N(R<sub>9</sub>)(R<sub>10</sub>);

 $Y_2$  is H<sub>2</sub> or O; $X_7$  is -N(R<sub>8</sub>)- or -O-;

25       each T<sub>1</sub> is independently selected from the group  
consisting of -O-, -S-, -S(O)-, and -S(O)<sub>2</sub>-;

$R_6$  is selected from the group consisting of -H and  
-CH<sub>3</sub>;

30        $R_8$  is selected from the group consisting of:



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- 5                   -C(O)-R<sub>10</sub>,  
                  -C(O)O-R<sub>9</sub>,  
                  -C(O)-NH-R<sub>10</sub>,  
                  -S(O)<sub>2</sub>-R<sub>9</sub>,  
                  -S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
                  -C(O)-CH<sub>2</sub>-OR<sub>10</sub>,  
                  -C(O)C(O)-R<sub>10</sub>,  
                  -C(O)-CH<sub>2</sub>-N(R<sub>10</sub>)(R<sub>10</sub>'),  
                  -C(O)-CH<sub>2</sub>C(O)-O-R<sub>9</sub>,  
10                   -C(O)-CH<sub>2</sub>C(O)-R<sub>9</sub>,  
                  -H, and  
                  -C(O)-C(O)-OR<sub>10</sub>;

                  each R<sub>9</sub> is independently selected from the group consisting of -Ar<sub>3</sub> and a -C<sub>1-6</sub> straight or branched  
15                   alkyl group optionally substituted with -Ar<sub>3</sub>, wherein the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

                  each R<sub>10</sub> is independently selected from the group consisting of -H, -Ar<sub>3</sub>, a -C<sub>3-6</sub> cycloalkyl group, and a  
                  -C<sub>1-6</sub> straight or branched alkyl group optionally  
20                   substituted with -Ar<sub>3</sub>, wherein the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

                  each R<sub>11</sub> is independently selected from the group consisting of:

- Ar<sub>4</sub>,  
25                   -(CH<sub>2</sub>)<sub>1-3</sub>-Ar<sub>4</sub>,  
                  -H, and  
                  -C(O)-Ar<sub>4</sub>;

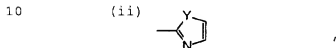
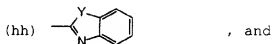
                  R<sub>15</sub> is selected from the group consisting of -OH, -OR<sub>3</sub>, -N(H)-OH, and -OC<sub>1-6</sub>, wherein C<sub>1-6</sub> is a straight  
30                   or branched alkyl group optionally substituted with

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$-\text{Ar}_3$ ,  $-\text{CONH}_2$ ,  $-\text{OR}_5$ ,  $-\text{OH}$ ,  $-\text{OR}_9$ , or  $-\text{CO}_2\text{H}$ ;

each  $\text{R}_{21}$  is independently selected from the group consisting of  $-\text{H}$  or a  $-\text{C}_{1-6}$  straight or branched alkyl group;

- 5             $\text{Ar}_2$  is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by  $-\text{Q}_1$  or phenyl, optionally substituted by  $\text{Q}_1$ :



wherein each Y is independently selected from the group consisting of O and S;

- each  $\text{Ar}_3$  is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{SO}-$ ,  $\text{SO}_2$ ,  $=\text{N}-$ , and  $-\text{NH}-$ ,  $-\text{N}(\text{R}_5)-$ , and  $-\text{N}(\text{R}_9)-$  said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by  $-\text{Q}_1$ ;

each  $\text{Ar}_4$  is a cyclic group independently selected

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from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said

5 heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, -NH-, -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings,

10 and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Q<sub>1</sub> is independently selected from the group consisting of -NH<sub>2</sub>, -CO<sub>2</sub>H, -Cl, -F, -Br, -I, -NO<sub>2</sub>, -CN, =O, -OH, -perfluoro C<sub>1-3</sub> alkyl, R<sub>5</sub>, -OR<sub>5</sub>, -NHR<sub>5</sub>, -OR<sub>9</sub>,

15 -N(R<sub>9</sub>)(R<sub>10</sub>), -R<sub>9</sub>, -C(O)-R<sub>10</sub>, and



20 provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub> group which comprises one or more additional -Ar<sub>3</sub> groups, said additional -Ar<sub>3</sub> groups are not substituted with another -Ar<sub>3</sub>.

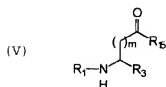
63. The compound according to claim 62,

25 wherein R<sub>1</sub> is (w2).

64. The compound according to claim 62, wherein R<sub>1</sub> is (e10-A).

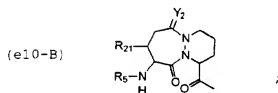
65. A compound represented by the formula:

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wherein:

m is 1 or 2;

5  $\text{R}_1$  is: $\text{R}_3$  is selected from the group consisting of:

- 10  $-\text{CN},$   
 $-\text{C}(\text{O})-\text{H},$   
 $-\text{C}(\text{O})-\text{CH}_2-\text{T}_1-\text{R}_{11},$   
 $-\text{C}(\text{O})-\text{CH}_2-\text{F},$   
 $-\text{C}=\text{N}-\text{O}-\text{R}_9,$  and  
 15  $-\text{CO}-\text{Ar}_2;$

each  $\text{R}_5$  is independently selected from the group consisting of:

- $-\text{C}(\text{O})-\text{R}_{10},$   
 $-\text{C}(\text{O})-\text{O}-\text{R}_9,$   
 20  $-\text{C}(\text{O})-\text{N}(\text{R}_{10})(\text{R}_{10})$   
 $-\text{S}(\text{O})_2-\text{R}_9,$   
 $-\text{S}(\text{O})_2-\text{NH}-\text{R}_{10},$   
 $-\text{C}(\text{O})-\text{CH}_2-\text{O}-\text{R}_9,$   
 $-\text{C}(\text{O})-\text{C}(\text{O})-\text{R}_{10},$   
 25  $-\text{R}_9,$   
 $-\text{H},$

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$\text{-C(O)C(O)-OR}_{10}$ , and  
 $\text{-C(O)C(O)-N(R}_9\text{)(R}_{10}\text{)}$ ;

$Y_2$  is  $H_2$  or  $O$ ;

5 each  $T_1$  is independently selected from the group consisting of  $-O-$ ,  $-S-$ ,  $-S(O)-$ , and  $-S(O)_2-$ ;

10 each  $R_9$  is independently selected from the group consisting of  $-\text{Ar}_3$  and a  $\text{-C}_{1-6}$  straight or branched alkyl group optionally substituted with  $-\text{Ar}_3$ , wherein the  $\text{-C}_{1-6}$  alkyl group is optionally unsaturated;

15 each  $R_{10}$  is independently selected from the group consisting of  $-H$ ,  $-\text{Ar}_3$ , a  $\text{-C}_{3-6}$  cycloalkyl group, and a  $\text{-C}_{1-6}$  straight or branched alkyl group optionally substituted with  $-\text{Ar}_3$ , wherein the  $\text{-C}_{1-6}$  alkyl group is optionally unsaturated;

each  $R_{11}$  is independently selected from the group consisting of:

20  $-\text{Ar}_4$ ,  
 $-(\text{CH}_2)_{1-3}-\text{Ar}_4$ ,  
 $-H$ , and  
 $-\text{C(O)-Ar}_4$ ;

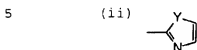
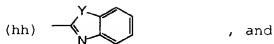
25  $R_{15}$  is selected from the group consisting of  $-\text{OH}$ ,  $-\text{OAr}_3$ ,  $-\text{N(H)-OH}$ , and  $-\text{OC}_{1-6}$ , wherein  $\text{C}_{1-6}$  is a straight or branched alkyl group optionally substituted with  $-\text{Ar}_3$ ,  $-\text{CONH}_2$ ,  $-\text{OR}_5$ ,  $-\text{OH}$ ,  $-\text{OR}_9$ , or  $-\text{CO}_2\text{H}$ ;

$R_{21}$  is  $-\text{CH}_3$ ;

$\text{Ar}_2$  is independently selected from the following

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group, in which any ring may optionally be singly or multiply substituted by  $-Q_1$  or phenyl, optionally substituted by  $Q_1$ :



wherein each Y is independently selected from the group consisting of O and S;


each  $Ar_3$  is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-,  $SO_2$ , =N-, and -NH-, -N( $R_5$ )-, and -N( $R_9$ )- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

each  $Ar_4$  is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-,  $SO_2$ , =N-, -NH-, -N( $R_5$ )-, and -N( $R_9$ )- said heterocycle group optionally

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containing one or more double bonds, said heterocyclic group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

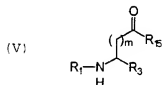
5 each  $Q_1$  is independently selected from the group consisting of  $-\text{NH}_2$ ,  $-\text{CO}_2\text{H}$ ,  $-\text{Cl}$ ,  $-\text{F}$ ,  $-\text{Br}$ ,  $-\text{I}$ ,  $-\text{NO}_2$ ,  $-\text{CN}$ ,  $=\text{O}$ ,  $-\text{OH}$ ,  $-\text{perfluoro C}_{1-3}$  alkyl,  $\text{R}_5$ ,  $-\text{OR}_5$ ,  $-\text{NHR}_5$ ,  $-\text{OR}_9$ ,  $-\text{N}(\text{R}_9)(\text{R}_{10})$ ,  $-\text{R}_9$ ,  $-\text{C}(\text{O})-\text{R}_{10}$ , and

10 

provided that when  $-\text{Ar}_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-\text{Ar}_3$  groups, said additional  $-\text{Ar}_3$  groups are not substituted with another  $-\text{Ar}_3$ .

15

66. A compound represented by the formula:

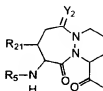


wherein:

20 m is 1 or 2;

$\text{R}_1$  is:

(e10-B)



25  $\text{R}_3$  is selected from the group consisting of:  
 $-\text{CN}$ ,

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-C(O)-H,  
-C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>,  
-C(O)-CH<sub>2</sub>-F,  
-C=N-O-R<sub>9</sub>, and  
5 -CO-Ar<sub>2</sub>;

each R<sub>5</sub> is -C(O)C(O)-OR<sub>10</sub>;

Y<sub>2</sub> is H<sub>2</sub> or O;

each T<sub>1</sub> is independently selected from the group  
10 consisting of -O-, -S-, -S(O)-, and -S(O)<sub>2</sub>-;

each R<sub>9</sub> is independently selected from the group  
consisting of -Ar<sub>3</sub> and a -C<sub>1-6</sub> straight or branched  
alkyl group optionally substituted with -Ar<sub>3</sub>, wherein  
the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

15 each R<sub>10</sub> is independently selected from the group  
consisting of -H, -Ar<sub>3</sub>, a -C<sub>3-6</sub> cycloalkyl group, and a  
-C<sub>1-6</sub> straight or branched alkyl group optionally  
substituted with -Ar<sub>3</sub>, wherein the -C<sub>1-6</sub> alkyl group is  
optionally unsaturated;

20 each R<sub>11</sub> is independently selected from the group  
consisting of:

-Ar<sub>4</sub>,  
-(CH<sub>2</sub>)<sub>1-3</sub>-Ar<sub>4</sub>,  
-H, and  
25 -C(O)-Ar<sub>4</sub>;

R<sub>15</sub> is selected from the group consisting of -OH,  
-OAr<sub>3</sub>, -N(H)-OH, and -OC<sub>1-6</sub>, wherein C<sub>1-6</sub> is a straight  
or branched alkyl group optionally substituted with

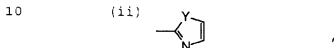
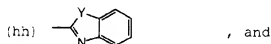


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$-\text{Ar}_3$ ,  $-\text{CONH}_2$ ,  $-\text{OR}_5$ ,  $-\text{OH}$ ,  $-\text{OR}_9$ , or  $-\text{CO}_2\text{H}$ ;

each  $\text{R}_{21}$  is independently selected from the group consisting of  $-\text{H}$  or a  $-\text{C}_{1-6}$  straight or branched alkyl group;

5  $\text{Ar}_2$  is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by  $-\text{Q}_1$  or phenyl, optionally substituted by  $\text{Q}_1$ :



wherein each Y is independently selected from the group consisting of O and S;

each  $\text{Ar}_3$  is a cyclic group independently selected  
 15 from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom  
 20 group selected from  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{SO}-$ ,  $\text{SO}_2$ ,  $=\text{N}-$ , and  $-\text{NH}-$ ,  $-\text{N}(\text{R}_5)-$ , and  $-\text{N}(\text{R}_9)-$  said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or  
 25 multiply substituted by  $-\text{Q}_1$ ;

each  $\text{Ar}_4$  is a cyclic group independently selected

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from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said  
 5 heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, -NH-, -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings,  
 10 and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

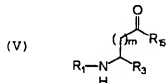
each Q<sub>1</sub> is independently selected from the group consisting of -NH<sub>2</sub>, -CO<sub>2</sub>H, -Cl, -F, -Br, -I, -NO<sub>2</sub>, -CN, =O, -OH, -perfluoro C<sub>1-3</sub> alkyl, R<sub>5</sub>, -OR<sub>5</sub>, -NHR<sub>5</sub>, -OR<sub>9</sub>,  
 15 -N(R<sub>9</sub>)(R<sub>10</sub>), -R<sub>9</sub>, -C(O)-R<sub>10</sub>, and

$$\begin{array}{c} \text{O} \\ / \quad \backslash \\ \quad \text{CH}_2 \\ \backslash \quad / \\ \text{O} \end{array}$$

20 provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub> group which comprises one or more additional -Ar<sub>3</sub> groups, said additional -Ar<sub>3</sub> groups are not substituted with another -Ar<sub>3</sub>.

67. The compound according to claim 66,  
 25 wherein R<sub>21</sub> is -CH<sub>3</sub>.

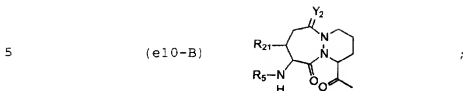
68. A compound represented by the formula:



wherein:

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m is 1 or 2;

 $R_1$  is: $R_3$  is selected from the group consisting of:

- CN,  
 -C(O)-H,  
 10 -C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>,  
 -C(O)-CH<sub>2</sub>-F,  
 -C=N-O-R<sub>9</sub>, and  
 -CO-Ar<sub>2</sub>;

each  $R_5$  is independently selected from the group  
 15 consisting of:

- C(O)-R<sub>10</sub>,  
 -C(O)O-R<sub>9</sub>,  
 -C(O)-N(R<sub>10</sub>)(R<sub>10</sub>)  
 -S(O)<sub>2</sub>-R<sub>9</sub>,  
 20 -S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
 -C(O)-CH<sub>2</sub>-O-R<sub>9</sub>,  
 -C(O)C(O)-R<sub>10</sub>,  
 -R<sub>9</sub>,  
 -H,  
 25 -C(O)C(O)-OR<sub>10</sub>, and  
 -C(O)C(O)-N(R<sub>9</sub>)(R<sub>10</sub>);

 $Y_2$  is H<sub>2</sub> or O;

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each  $T_1$  is independently selected from the group consisting of -O-, -S-, -S(O)-, and -S(O)<sub>2</sub>-;

5 each  $R_9$  is independently selected from the group consisting of -Ar<sub>3</sub> and a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with -Ar<sub>3</sub>, wherein the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

10 each  $R_{10}$  is independently selected from the group consisting of -H, -Ar<sub>3</sub>, a -C<sub>3-6</sub> cycloalkyl group, and a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with -Ar<sub>3</sub>, wherein the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

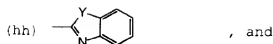
15 each  $R_{11}$  is independently selected from the group consisting of:  
-Ar<sub>4</sub>,  
-(CH<sub>2</sub>)<sub>1-3</sub>-Ar<sub>4</sub>,  
-H, and  
-C(O)-Ar<sub>4</sub>;

20  $R_{15}$  is selected from the group consisting of -OH, -OAr<sub>3</sub>, -N(H)-OH, and -OC<sub>1-6</sub>, wherein C<sub>1-6</sub> is a straight or branched alkyl group optionally substituted with -Ar<sub>3</sub>, -CONH<sub>2</sub>, -OR<sub>5</sub>, -OH, -OR<sub>9</sub>, or -CO<sub>2</sub>H;

25 each  $R_{21}$  is independently selected from the group consisting of -H or a -C<sub>1-6</sub> straight or branched alkyl group;

Ar<sub>2</sub> is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by -Q<sub>1</sub> or phenyl, optionally substituted by Q<sub>1</sub>:

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wherein each Y is independently selected from the  
 5 group consisting of O and S;

each Ar<sub>3</sub> is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5  
 10 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, and -NH-, -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally containing one or more double bonds, said heterocycle  
 15 group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Ar<sub>4</sub> is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3  
 20 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, -NH-,  
 25 -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

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each  $Q_1$  is independently selected from the group consisting of  $-\text{NH}_2$ ,  $-\text{CO}_2\text{H}$ ,  $-\text{Cl}$ ,  $-\text{F}$ ,  $-\text{Br}$ ,  $-\text{I}$ ,  $-\text{NO}_2$ ,  $-\text{CN}$ ,  $=\text{O}$ ,  $-\text{OH}$ ,  $-\text{perfluoro C}_{1-3}$  alkyl,  $\text{R}_5$ ,  $-\text{OR}_5$ ,  $-\text{NHR}_5$ ,  $-\text{OR}_9$ ,  $-\text{N}(\text{R}_9)(\text{R}_{10})$ ,  $-\text{R}_9$ ,  $-\text{C}(\text{O})-\text{R}_{10}$ , and

5



provided that when  $-\text{Ar}_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-\text{Ar}_3$  groups, said additional  $-\text{Ar}_3$  groups are not substituted with another  $-\text{Ar}_3$ ;

provided that when:

$m$  is 1;

15  $\text{R}_{15}$  is  $-\text{OH}$ ;

$\text{R}_{21}$  is  $-\text{H}$ ; and

$\text{Y}_2$  is  $\text{O}$  and  $\text{R}_3$  is  $-\text{C}(\text{O})-\text{H}$ , then  $\text{R}_5$  cannot be:  
 $-\text{C}(\text{O})-\text{R}_{10}$ , wherein  $\text{R}_{10}$  is  $-\text{Ar}_3$  and the  $\text{Ar}_3$  cyclic group is phenyl, unsubstituted by  $-\text{Q}_1$ , 4-  
 20 (carboxymethoxy)phenyl, 2-fluorophenyl, 2-pyridyl, N-(4-methylpiperazino)methylphenyl, or

$-\text{C}(\text{O})-\text{OR}_9$ , wherein  $\text{R}_9$  is  $-\text{CH}_2-\text{Ar}_3$ , and the  $\text{Ar}_3$  cyclic group is phenyl, unsubstituted by  $-\text{Q}_1$ ; and when

$\text{Y}_2$  is  $\text{O}$ ,  $\text{R}_3$  is  $-\text{C}(\text{O})-\text{CH}_2-\text{T}_1-\text{R}_{11}$ ,  $\text{T}_1$  is  $\text{O}$ , and  $\text{R}_{11}$   
 25 is  $\text{Ar}_4$ , wherein the  $\text{Ar}_4$  cyclic group is 5-(1-(4-chlorophenyl)-3-trifluoromethyl)pyrazolyl, then  $\text{R}_5$  cannot be:

$-\text{H}$ ;

$-\text{C}(\text{O})-\text{R}_{10}$ , wherein  $\text{R}_{10}$  is  $-\text{Ar}_3$  and the  $\text{Ar}_3$  cyclic group is 4-(dimethylaminomethyl)phenyl, phenyl, 4-  
 30 (carboxymethylthio)phenyl, 4-(carboxyethylthio)phenyl,

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4-(carboxyethyl)phenyl, 4-(carboxypropyl)phenyl, 2-fluorophenyl, 2-pyridyl, N-(4-methylpiperazino)methylphenyl, or

5       -C(O)-OR<sub>9</sub>, wherein R<sub>9</sub> is isobutyl or -CH<sub>2</sub>-Ar<sub>3</sub> and the Ar<sub>3</sub> cyclic group is phenyl;

and when R<sub>11</sub> is Ar<sub>4</sub>, wherein the Ar<sub>4</sub> cyclic group is 5-(1-phenyl-3-trifluoromethyl)pyrazolyl or 5-(1-(4-chloro-2-pyridinyl)-3-trifluoromethyl)pyrazolyl, then R<sub>5</sub> cannot be:

10       -C(O)-OR<sub>9</sub>, wherein R<sub>9</sub> is -CH<sub>2</sub>-Ar<sub>3</sub>, and the Ar<sub>3</sub> cyclic group is phenyl;

and when R<sub>11</sub> is Ar<sub>4</sub>, wherein the Ar<sub>4</sub> cyclic group is 5-(1-(2-pyridyl)-3-trifluoromethyl)pyrazolyl, then R<sub>5</sub> cannot be:

15       -C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is -Ar<sub>3</sub> and the Ar<sub>3</sub> cyclic group is 4-(dimethylaminomethyl)phenyl, or

-C(O)-OR<sub>9</sub>, wherein R<sub>9</sub> is -CH<sub>2</sub>-Ar<sub>3</sub>, and the Ar<sub>3</sub> cyclic group is phenyl, unsubstituted by -Q<sub>1</sub>; and when

20       Y<sub>2</sub> is O, R<sub>3</sub> is -C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>, T<sub>1</sub> is O, and R<sub>11</sub> is -C(O)-Ar<sub>4</sub>, wherein the Ar<sub>4</sub> cyclic group is 2,5-dichlorophenyl, then R<sub>5</sub> cannot be:

25       -C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is -Ar<sub>3</sub> and the Ar<sub>3</sub> cyclic group is 4-(dimethylaminomethyl)phenyl, 4-(N-morpholinomethyl)phenyl, 4-(N-methylpiperazino)methylphenyl, 4-(N-(2-methylimidazolyl)methyl)phenyl, 5-benzimidazolyl, 5-benzotriazolyl, N-carboethoxy-5-benzotriazolyl, N-carboethoxy-5-benzimidazolyl, or

30       -C(O)-OR<sub>9</sub>, wherein R<sub>9</sub> is -CH<sub>2</sub>-Ar<sub>3</sub>, and the Ar<sub>3</sub> cyclic group is phenyl, unsubstituted by -Q<sub>1</sub>; and when

Y<sub>2</sub> is H<sub>2</sub>, R<sub>3</sub> is -C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>, T<sub>1</sub> is O, and R<sub>11</sub>

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is  $-C(O)-Ar_4$ , wherein the  $Ar_4$  cyclic group is 2,5-dichlorophenyl, then  $R_5$  cannot be:

$-C(O)-OR_9$ , wherein  $R_9$  is  $-CH_2-Ar_3$  and the  $Ar_3$  cyclic group is phenyl.

5                    69. The compound according to claim 68, wherein  $R_{21}$  is  $-CH_3$ .

70. The compound according to claim 68, wherein  $R_5$  is  $-C(O)-C(O)-OR_{10}$ .

10                   71. The compound according to claim 68, wherein  $R_5$  is  $-C(O)-C(O)-OR_{10}$  and  $R_{21}$  is  $-CH_3$ .

72. The compound according to any one of claims 66, 67, 70 and 71, wherein  $R_3$  is  $-C(O)-H$ .

73. The compound according to any one of claims 65, 68 and 69, wherein  $R_3$  is  $-C(O)-H$ .

15                   74. The compound according to claim 68, wherein:

$R_3$  is  $-C(O)-H$ , and

$R_5$  is  $-C(O)-R_{10}$ , wherein:

20                    $R_{10}$  is  $Ar_3$ , wherein the  $Ar_3$  cyclic group is phenyl optionally being singly or multiply substituted by:

$-F$ ,

$-Cl$ ,

25                    $-N(H)-R_5$ , wherein  $-R_5$  is  $-H$  or  $-C(O)-R_{10}$ , wherein  $R_{10}$  is a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $-Ar_3$ , wherein  $Ar_3$  is



- 833 -

phenyl,

-N(R<sub>9</sub>)(R<sub>10</sub>), wherein R<sub>9</sub> and R<sub>10</sub> are independently a  
-C<sub>1-4</sub> straight or branched alkyl group, or

-O-R<sub>5</sub>, wherein R<sub>5</sub> is H or a -C<sub>1-4</sub> straight or  
5 branched alkyl group.

75. The compound according to claim 74,  
wherein Ar<sub>3</sub> is phenyl being optionally singly or  
multiply substituted at the 3- or 5-position by -Cl or  
at the 4-position by -NH-R<sub>5</sub>, -N(R<sub>9</sub>)(R<sub>10</sub>), or -O-R<sub>5</sub>.

10 76. The compound according to claim 68,  
wherein:

R<sub>3</sub> is -C(O)-H;

R<sub>5</sub> is -C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is Ar<sub>3</sub> and the Ar<sub>3</sub>  
cyclic group is selected from the group consisting of  
15 is indolyl, benzimidazolyl, thienyl, and  
benzo[b]thiophenyl, and said cyclic group optionally  
being singly or multiply substituted by -Q<sub>1</sub>.

77. The compound according to claim 68,  
wherein:

20 R<sub>3</sub> is -C(O)-H; and

R<sub>5</sub> is -C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is Ar<sub>3</sub> and the Ar<sub>3</sub>  
cyclic group is selected from quinolyl and isoquinolyl,  
and said cyclic group optionally being singly or  
multiply substituted by -Q<sub>1</sub>.

25 78. The compound according to claim 68,  
wherein:

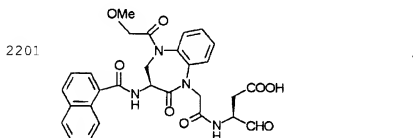
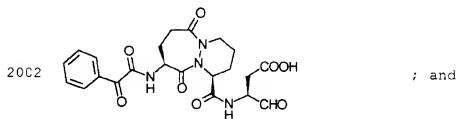
- 884 -

$R_3$  is  $-C(O)-H$ ; and

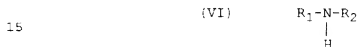
$R_5$  is  $-C(O)-R_{10}$ , wherein  $R_{10}$  is  $Ar_3$  and the  $Ar_3$  cyclic group is phenyl, substituted by



79. The compound according to claim 68,  
10 selected from the group consisting of:



80. A compound represented by the formula:

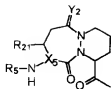


wherein:

$R_1$  is:

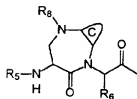
- 885 -

(e10)



, or

(w2)



;

- 5 C is a ring chosen from the set consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl; the ring optionally being singly or multiply substituted by  $-Q_1$ ;

10

 $R_2$  is:

(a)



, or

(b)



;

 $m$  is 1 or 2;

15

each  $R_5$  is independently selected from the group consisting of:

- C(O)- $R_{10}$ ,
- C(O)-O- $R_g$ ,
- C(O)-N( $R_{10}$ )( $R_{10}$ )

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- 5                   -S(O)<sub>2</sub>-R<sub>9</sub>,  
                  -S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
                  -C(O)-CH<sub>2</sub>-O-R<sub>9</sub>,  
                  -C(O)C(O)-R<sub>10</sub>,  
                  -R<sub>9</sub>,  
                  -H,  
                  -C(O)C(O)-OR<sub>10</sub>, and  
                  -C(O)C(O)-N(R<sub>9</sub>)(R<sub>10</sub>);
- 10           X<sub>5</sub> is CH or N;
- Y<sub>2</sub> is H<sub>2</sub> or O;
- R<sub>6</sub> is selected from the group consisting of -H and
- 15           -CH<sub>3</sub>;
- R<sub>8</sub> is selected from the group consisting of:
- C(O)-R<sub>10</sub>,  
                  -C(O)O-R<sub>9</sub>,  
                  -C(O)-N(H)-R<sub>10</sub>,  
20               -S(O)<sub>2</sub>-R<sub>9</sub>,  
                  -S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
                  -C(O)-CH<sub>2</sub>-OR<sub>10</sub>,  
                  -C(O)C(O)-R<sub>10</sub>;  
                  -C(O)-CH<sub>2</sub>N(R<sub>10</sub>)(R<sub>10</sub>),  
25               -C(O)-CH<sub>2</sub>C(O)-O-R<sub>9</sub>,  
                  -C(O)-CH<sub>2</sub>C(O)-R<sub>9</sub>,  
                  -H, and  
                  -C(O)-C(O)-OR<sub>10</sub>;
- 30           each R<sub>9</sub> is independently selected from the group  
              consisting of -Ar<sub>3</sub> and a -C<sub>1-6</sub> straight or branched  
              alkyl group optionally substituted with -Ar<sub>3</sub>, wherein  
              the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

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each  $R_{10}$  is independently selected from the group consisting of -H,  $-Ar_3$ , a  $-C_{3-6}$  cycloalkyl group, and a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $-Ar_3$ , wherein the  $-C_{1-6}$  alkyl group is optionally unsaturated;

$R_{13}$  is selected from the group consisting of H,  $Ar_3$ , and a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $-Ar_3$ ,  $-CONH_2$ ,  $-OR_5$ ,  $-OH$ ,  $-OR_9$ , or  $-CO_2H$ ;

each  $R_{51}$  is independently selected from the group consisting of  $R_9$ ,  $-C(O)-R_9$ ,  $-C(O)-N(H)-R_9$ , or each  $R_{51}$  taken together forms a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-;

each  $R_{21}$  is independently selected from the group consisting of -H or a  $-C_{1-6}$  straight or branched alkyl group;

each  $Ar_3$  is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-,  $SO_2$ , =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

each  $Q_1$  is independently selected from the group

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consisting of  $-\text{NH}_2$ ,  $-\text{CO}_2\text{H}$ ,  $-\text{Cl}$ ,  $-\text{F}$ ,  $-\text{Br}$ ,  $-\text{I}$ ,  $-\text{NO}_2$ ,  $-\text{CN}$ ,  
 $=\text{O}$ ,  $-\text{OH}$ ,  $-\text{perfluoro C}_{1-3}$  alkyl,  $\text{R}_5$ ,  $-\text{OR}_5$ ,  $-\text{NHR}_5$ ,  $-\text{OR}_9$ ,  
 $-\text{N}(\text{R}_9)(\text{R}_{10})$ ,  $-\text{R}_9$ ,  $-\text{C}(\text{O})-\text{R}_{10}$ , and

5



provided that when  $-\text{Ar}_3$  is substituted with a  $\text{Q}_1$   
 10 group which comprises one or more additional  $-\text{Ar}_3$   
 groups, said additional  $-\text{Ar}_3$  groups are not substituted  
 with another  $-\text{Ar}_3$ .

81. The compound according to claim 80,  
 wherein:

15 m is 1;

C is a ring chosen from the set consisting of  
 benzo, pyrido, or thieno the ring optionally being  
 singly or multiply substituted by halogen,  $-\text{NH}_2$ ,  
 $-\text{NH}-\text{R}_5$ ,  $-\text{NH}-\text{R}_9$ ,  $-\text{OR}_{10}$ , or  $-\text{R}_9$ , wherein  $\text{R}_9$  is a straight  
 20 or branched  $\text{C}_{1-4}$  alkyl group, and  $\text{R}_{10}$  is H or a straight  
 or branched  $\text{C}_{1-4}$  alkyl group;

$\text{R}_6$  is H;

$\text{R}_{13}$  is H or a  $\text{C}_{1-4}$  straight or branched alkyl group  
 optionally substituted with  $-\text{Ar}_3$ ,  $-\text{OH}$ ,  $-\text{OR}_9$ ,  $-\text{CO}_2\text{H}$ ,  
 25 wherein the  $\text{R}_9$  is a  $\text{C}_{1-4}$  branched or straight chain  
 alkyl group; wherein  $\text{Ar}_3$  is morpholinyl or phenyl,  
 wherein the phenyl is optionally substituted by  $-\text{Q}_1$ ;

$\text{R}_{21}$  is  $-\text{H}$  or  $-\text{CH}_3$ ;

$\text{R}_{51}$  is a  $\text{C}_{1-6}$  straight or branched alkyl group

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optionally substituted with  $-\text{Ar}_3$ , wherein  $\text{Ar}_3$  is phenyl, optionally substituted by  $-\text{Q}_1$ ;

each  $\text{Ar}_3$  cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinoliny, isoquinoliny, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by  $-\text{Q}_1$ ;

each  $\text{Q}_1$  is independently selected from the group consisting of  $-\text{NH}_2$ ,  $-\text{Cl}$ ,  $-\text{F}$ ,  $-\text{Br}$ ,  $-\text{OH}$ ,  $-\text{R}_9$ ,  $-\text{NH}-\text{R}_5$  wherein  $\text{R}_5$  is  $-\text{C}(\text{O})-\text{R}_{10}$  or  $-\text{S}(\text{O})_2-\text{R}_9$ ,  $-\text{OR}_5$  wherein  $\text{R}_5$  is  $-\text{C}(\text{O})-\text{R}_{10}$ ,  $-\text{OR}_9$ ,  $-\text{NHR}_9$ , and



wherein each  $\text{R}_9$  and  $\text{R}_{10}$  are independently a  $-\text{C}_{1-6}$  straight or branched alkyl group optionally substituted with  $-\text{Ar}_3$  wherein  $\text{Ar}_3$  is phenyl;

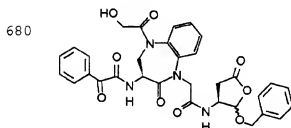
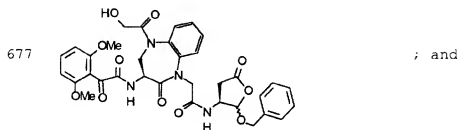
provided that when  $-\text{Ar}_3$  is substituted with a  $\text{Q}_1$  group which comprises one or more additional  $-\text{Ar}_3$  groups, said additional  $-\text{Ar}_3$  groups are not substituted with another  $-\text{Ar}_3$ .

82. The compound according to claim 81, wherein  $\text{R}_1$  is (w2).

83. The compound according to claim 82,

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selected from the group consisting of:



84. The compound according to claim 82,  
5 wherein  $R_8$  is selected from the group consisting of:

- C(O)- $R_{10}$ ,
- C(O)O- $R_9$ ,
- C(O)-CH<sub>2</sub>-OR<sub>10</sub>, and
- C(O)-CH<sub>2</sub>C(O)- $R_9$ .

10 85. The compound according to claim 84,  
wherein  $R_8$  is -C(O)-CH<sub>2</sub>-OR<sub>10</sub> and  $R_{10}$  is -H or -CH<sub>3</sub>.

86. The compound according to claim 81,  
wherein  $R_1$  is (e10) and  $X_5$  is CH.

15 87. The compound according to claim 81,  
wherein  $R_1$  is (e10) and  $X_5$  is N.

88. The compound according to any one of  
claims 80-87 wherein  $R_5$  is -C(O)- $R_{10}$  or -C(O)-C(O)- $R_{10}$ .



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89. The compound according to claim 88,  
wherein  $R_{10}$  is  $Ar_3$ .

90. The compound according to claim 89,  
wherein:

5  $R_5$  is  $-C(O)-R_{10}$  and  $R_{10}$  is  $Ar_3$ , wherein the  $Ar_3$   
cyclic group is phenyl optionally being singly or  
multiply substituted by:

$-R_9$ , wherein  $R_9$  is a  $C_{1-4}$  straight or branched  
alkyl group;

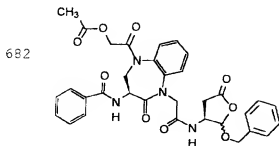
10  $-F$ ,  
 $-Cl$ ,

$-N(H)-R_5$ , wherein  $-R_5$  is  $-H$  or  $-C(O)-R_{10}$ , wherein  
 $R_{10}$  is a  $-C_{1-6}$  straight or branched alkyl group  
optionally substituted with  $-Ar_3$ , wherein  $Ar_3$  is  
15 phenyl,

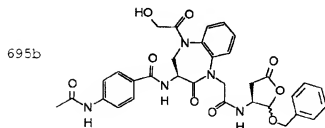
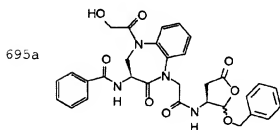
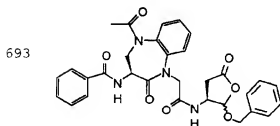
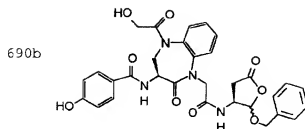
$-N(R_9)(R_{10})$ , wherein  $R_9$  and  $R_{10}$  are independently a  
 $-C_{1-4}$  straight or branched alkyl group, or

$-O-R_5$ , wherein  $R_5$  is  $H$  or a  $-C_{1-4}$  straight or  
branched alkyl group.

20 91. The compound according to claim 90,  
selected from the group consisting of:



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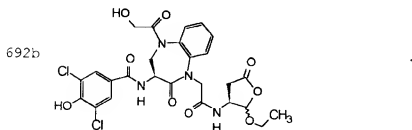
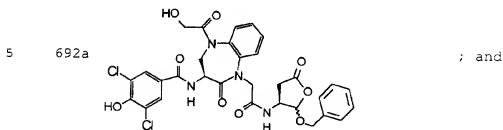
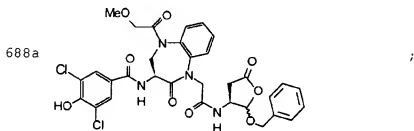
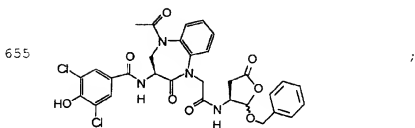


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92. The compound according to claim 90, wherein  $Ar_3$  is phenyl being singly or multiply substituted at the 3- or 5-position by -Cl or at the 4-position by -NH-R<sub>5</sub>, -N(R<sub>9</sub>)(R<sub>10</sub>), or -O-R<sub>5</sub>.

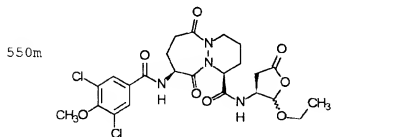
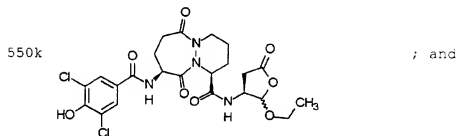
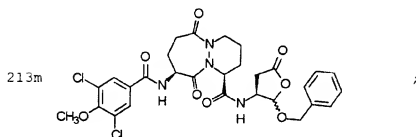
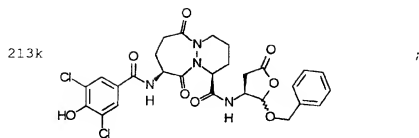
- 893 -

93. The compound according to claim 92,  
selected from the group consisting of:



94. The compound according to claim 92,  
selected from the group consisting of:

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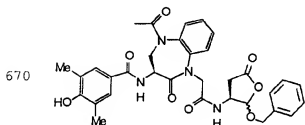


- 5                    95. The compound according to claim 90,  
 wherein Ar<sub>3</sub> is phenyl being singly or multiply  
 substituted at the 3- or 5-position by -R<sub>9</sub>, wherein R<sub>9</sub>  
 is a C<sub>1-4</sub> straight or branched alkyl group;

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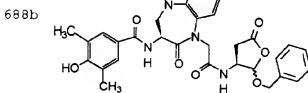
and at the 4-position by -O-R<sub>5</sub>.

96. The compound according to claim 95, selected from the group consisting of:



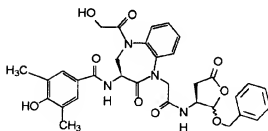
;

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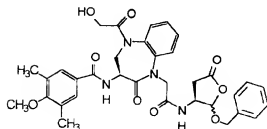
;

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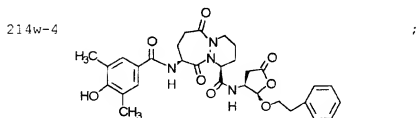
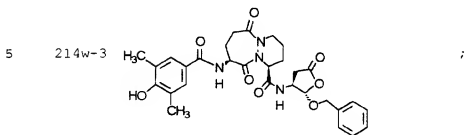
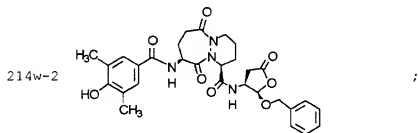
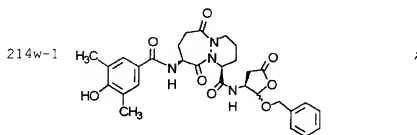
; and

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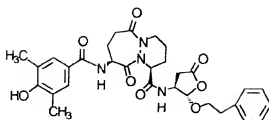
- 896 -

97. The compound according to claim 95,  
selected from the group consisting of:



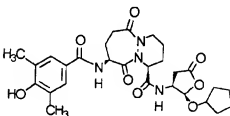
- 897 -

214w-5



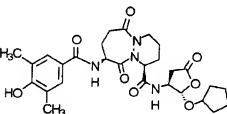
;

214w-6



; and

214w-7



.

98. The compound according to claim 89,

5 wherein:

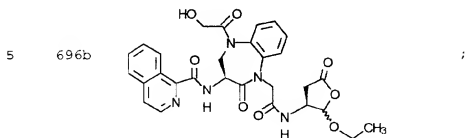
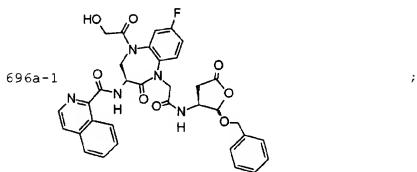
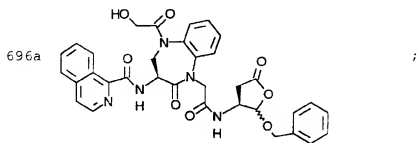
$R_5$  is  $-C(O)-R_{10}$ , wherein  $R_{10}$  is  $Ar_3$  and the  $Ar_3$  cyclic group is selected from the group consisting of is indolyl, benzimidazolyl, thienyl, quinolyl, isoquinolyl and benzo[b]thiophenyl, and said cyclic  
 10 group optionally being singly or multiply substituted by  $-Q_1$ .

99. The compound according to claim 98,

wherein the  $Ar_3$  cyclic group is isoquinolyl, and said cyclic group optionally being singly or multiply  
 15 substituted by  $-Q_1$ .

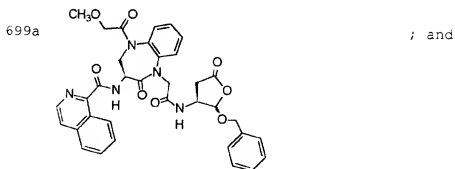
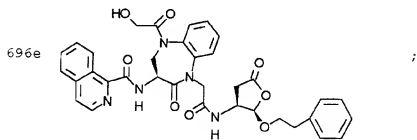
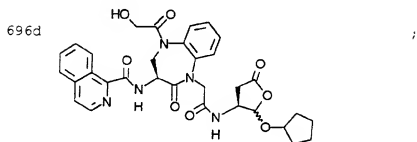
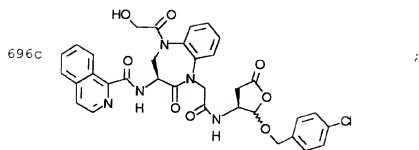
- 898 -

100. The compound according to claim 99  
selected from the group consisting of:

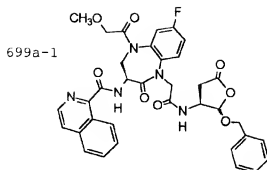




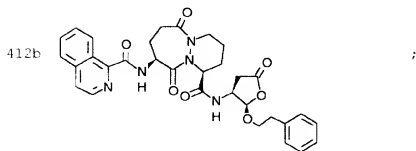
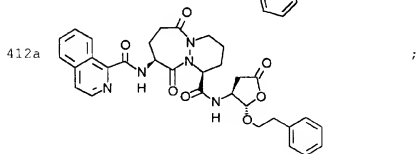
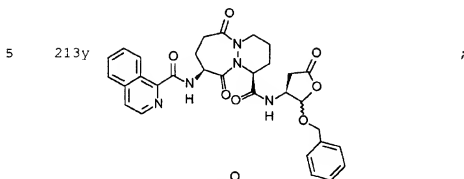
- 899 -



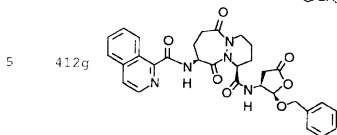
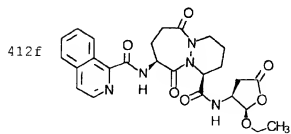
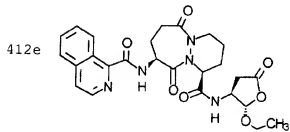
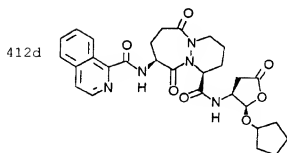
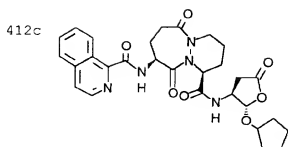
- 900 -



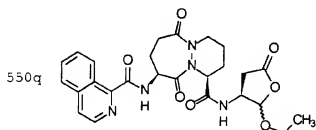
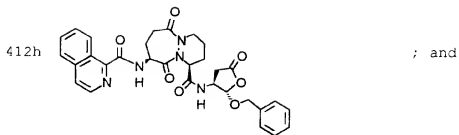
101. The compound according to claim 99,  
selected from the group consisting of:



- 901 -



- 902 -

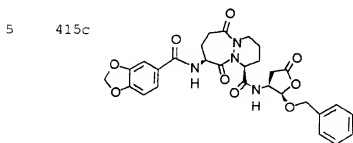
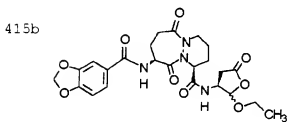
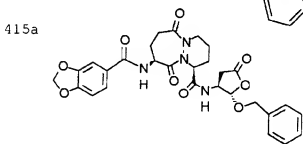
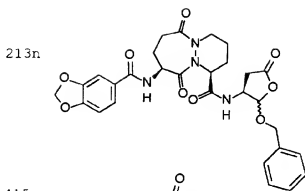


102. The compound according to claim 89,  
 wherein  $R_5$  is  $-C(O)-R_{10}$ , wherein  $R_{10}$  is  $Ar_3$  and the  $Ar_3$   
 5 cyclic group is phenyl, substituted by



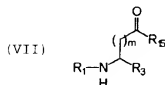
103. The compound according to claim 102,  
 selected from the group consisting of:

- 903 -



- 904 -

104. A compound represented by the formula:

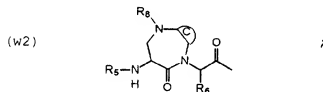


wherein:

m is 1 or 2;

5

R<sub>1</sub> is selected from the group consisting of the following formulae:



10

C is a ring chosen from the set consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl, the ring optionally being  
 15 singly or multiply substituted by -Q<sub>1</sub>;

R<sub>3</sub> is selected from the group consisting of:

-CN,  
 -C(O)-H,  
 -C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>,  
 20 -C(O)-CH<sub>2</sub>-F,  
 -C=N-O-R<sub>9</sub>, and  
 -CO-Ar<sub>2</sub>;

each R<sub>5</sub> is independently selected from the group consisting of:

25

-C(O)-R<sub>10</sub>,

- 905 -

-C(O)O-R<sub>9</sub>,  
 -C(O)-N(R<sub>10</sub>)(R<sub>10</sub>)  
 -S(O)<sub>2</sub>-R<sub>9</sub>,  
 -S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
 5    -C(O)-CH<sub>2</sub>-O-R<sub>9</sub>,  
       -C(O)C(O)-R<sub>10</sub>,  
       -R<sub>9</sub>,  
       -H,  
       -C(O)C(O)-OR<sub>10</sub>, and  
 10    -C(O)C(O)-N(R<sub>9</sub>)(R<sub>10</sub>);

each T<sub>1</sub> is independently selected from the group consisting of -O-, -S-, -S(O)-, and -S(O)<sub>2</sub>-;

15    R<sub>6</sub> is selected from the group consisting of -H and -CH<sub>3</sub>;

R<sub>8</sub> is selected from the group consisting of:

-C(O)-R<sub>10</sub>,  
 -C(O)O-R<sub>9</sub>,  
 20    -C(O)-NH-R<sub>10</sub>,  
       -S(O)<sub>2</sub>-R<sub>9</sub>,  
       -S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
       -C(O)-CH<sub>2</sub>-OR<sub>10</sub>,  
       -C(O)C(O)-R<sub>10</sub>,  
 25    -C(O)-CH<sub>2</sub>-N(R<sub>10</sub>)(R<sub>10</sub>),  
       -C(O)-CH<sub>2</sub>C(O)-O-R<sub>9</sub>,  
       -C(O)-CH<sub>2</sub>C(O)-R<sub>9</sub>,  
       -H, and  
       -C(O)-C(O)-OR<sub>10</sub>;

30    each R<sub>9</sub> is independently selected from the group consisting of -Ar<sub>3</sub> and a -C<sub>1-6</sub> straight or branched

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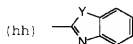
alkyl group optionally substituted with  $-\text{Ar}_3$ , wherein the  $-\text{C}_{1-6}$  alkyl group is optionally unsaturated;

each  $\text{R}_{10}$  is independently selected from the group consisting of  $-\text{H}$ ,  $-\text{Ar}_3$ , a  $-\text{C}_{3-6}$  cycloalkyl group, and a  
 5  $-\text{C}_{1-6}$  straight or branched alkyl group optionally substituted with  $-\text{Ar}_3$ , wherein the  $-\text{C}_{1-6}$  alkyl group is optionally unsaturated;

each  $\text{R}_{11}$  is independently selected from the group consisting of:  
 10  $-\text{Ar}_4$ ,  
 $-(\text{CH}_2)_{1-3}-\text{Ar}_4$ ,  
 $-\text{H}$ , and  
 $-\text{C}(\text{O})-\text{Ar}_4$ ;

$\text{R}_{15}$  is selected from the group consisting of  $-\text{OH}$ ,  
 15  $-\text{OAr}_3$ ,  $-\text{N}(\text{H})-\text{OH}$ , and  $-\text{OC}_{1-6}$ , wherein  $\text{C}_{1-6}$  is a straight or branched alkyl group optionally substituted with  $-\text{Ar}_3$ ,  $-\text{CONH}_2$ ,  $-\text{OR}_5$ ,  $-\text{OH}$ ,  $-\text{OR}_9$ , or  $-\text{CO}_2\text{H}$ ;

$\text{Ar}_2$  is independently selected from the following group, in which any ring may optionally be singly or  
 20 multiply substituted by  $-\text{Q}_1$  or phenyl, optionally substituted by  $\text{Q}_1$ :



, and



- 907 -

(ii)



wherein each Y is independently selected from the group consisting of O and S;

5           each Ar<sub>3</sub> is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said  
10       heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, and -NH-, -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings,  
15       and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

          each Ar<sub>4</sub> is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3  
20       rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, -NH-, -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally  
25       containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

          each Q<sub>1</sub> is independently selected from the group  
30       consisting of -NH<sub>2</sub>, -CO<sub>2</sub>H, -Cl, -F, -Br, -I, -NO<sub>2</sub>, -CN,

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=O, -OH, -perfluoro C<sub>1-3</sub> alkyl, R<sub>5</sub>, -OR<sub>5</sub>, -NHR<sub>5</sub>, -OR<sub>9</sub>,  
 -N(R<sub>9</sub>)(R<sub>10</sub>), -R<sub>9</sub>, -C(O)-R<sub>10</sub>, and

$$\begin{array}{c} \text{O} \\ / \quad \backslash \\ \quad \text{CH}_2 \\ \backslash \quad / \\ \text{O} \end{array}$$

5

provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub>  
 group which comprises one or more additional -Ar<sub>3</sub>  
 groups, said additional -Ar<sub>3</sub> groups are not substituted  
 10 with another -Ar<sub>3</sub>.

105. The compound according to claim 104,  
 wherein:

m is 1;

C is a ring chosen from the set consisting of  
 15 benzo, pyrido, and thieno, the ring optionally being  
 singly or multiply substituted by halogen, -NH<sub>2</sub>,  
 -NH-R<sub>5</sub>, or -NH-R<sub>9</sub>, -OR<sub>10</sub>, or -R<sub>9</sub>, wherein R<sub>9</sub> is a  
 straight or branched C<sub>1-4</sub> alkyl group, and R<sub>10</sub> is H or a  
 straight or branched C<sub>1-4</sub> alkyl group;

20

T<sub>1</sub> is O or S;

R<sub>6</sub> is H;

R<sub>11</sub> is selected from the group consisting of -Ar<sub>4</sub>,  
 -(CH<sub>2</sub>)<sub>1-3</sub>-Ar<sub>4</sub>, and -C(O)-Ar<sub>4</sub>;

25

Ar<sub>2</sub> is (hh);

Y is O;

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each Ar<sub>3</sub> cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, thiazolyl, benzimidazolyl, thienothienyl, thiadiazolyl, benzotriazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Ar<sub>4</sub> cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, naphthyl, pyridinyl, oxazolyl, pyrimidinyl, or indolyl, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Q<sub>1</sub> is independently selected from the group consisting of -NH<sub>2</sub>, -Cl, -F, -Br, -OH, -R<sub>9</sub>, -NH-R<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or -S(O)<sub>2</sub>-R<sub>9</sub>, -OR<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub>, -OR<sub>9</sub>, -NHR<sub>9</sub>, and



wherein each R<sub>9</sub> and R<sub>10</sub> are independently a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with -Ar<sub>3</sub> wherein Ar<sub>3</sub> is phenyl;

provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub> group which comprises one or more additional -Ar<sub>3</sub> groups, said additional -Ar<sub>3</sub> groups are not substituted with another -Ar<sub>3</sub>.

106. The compound according to claim 105, wherein R<sub>8</sub> is selected from the group consisting of:

- 910 -

-C(O)-R<sub>10</sub>,  
-C(O)O-R<sub>9</sub>,  
-C(O)-CH<sub>2</sub>-OR<sub>10</sub>, and  
-C(O)-CH<sub>2</sub>C(O)-R<sub>9</sub>.

5                    107. The compound according to claim 106,  
wherein R<sub>8</sub> is -C(O)-CH<sub>2</sub>-OR<sub>10</sub> and R<sub>10</sub> is -H or -CH<sub>3</sub>.

108. The compound according to claim 105,  
wherein R<sub>3</sub> is -C(O)-Ar<sub>2</sub>,

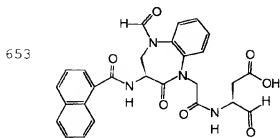
109. The compound according to claim 105,  
10                    wherein R<sub>3</sub> is -C(O)CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>;

110. The compound according to claim 105,  
wherein R<sub>3</sub> is -C(O)-H.

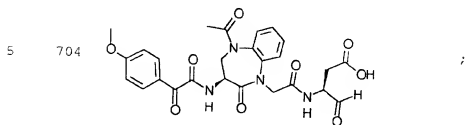
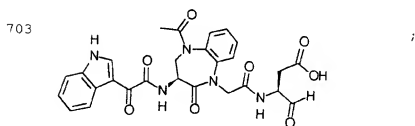
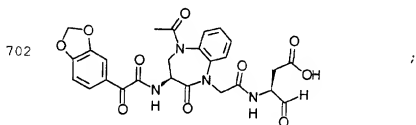
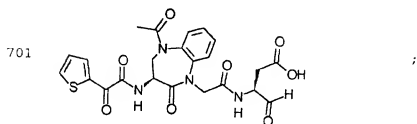
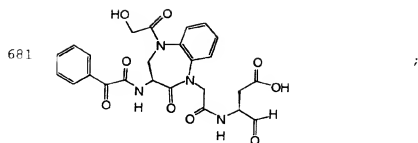
111. The compound according to claim 110,  
wherein R<sub>8</sub> is selected from the group consisting of:

15                    -C(O)-R<sub>10</sub>,  
                     -C(O)O-R<sub>9</sub>,  
                     -C(O)-CH<sub>2</sub>-OR<sub>10</sub>, and  
                     -C(O)-CH<sub>2</sub>C(O)-R<sub>9</sub>.

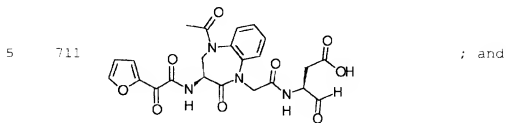
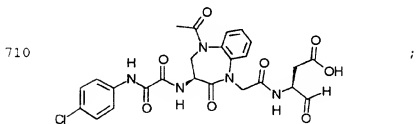
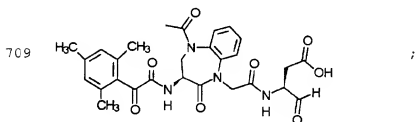
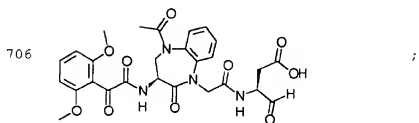
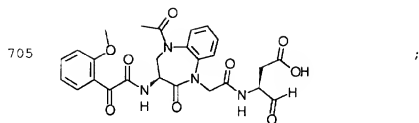
112. The compound according to claim 111,  
20                    selected from the group consisting of:



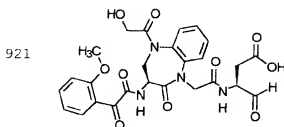
- 911 -



- 912 -



- 913 -



113. The compound according to claim 111,  
wherein  $R_8$  is  $-C(O)-CH_2-OR_{10}$  and  $R_{10}$  is  $-H$  or  $-CH_3$ .

114. The compound according to claim 68,  
5 wherein:

$m$  is 1;

$T_1$  is O or S;

$R_{21}$  is  $-H$  or  $-CH_3$ ;

10  $Ar_2$  is (hh);

$Y$  is O;

each  $Ar_3$  cyclic group is independently selected  
from the set consisting of phenyl, naphthyl, thienyl,  
15 quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl,  
isoxazolyl, benzotriazolyl, benzimidazolyl,  
thienothienyl, imidazolyl, thiadiazolyl,  
benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl  
and said cyclic group being singly or multiply  
20 substituted by  $-Q_1$ ;

each  $Ar_4$  cyclic group is independently selected  
from the set consisting of phenyl, tetrazolyl,  
pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl

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and said cyclic group being singly or multiply substituted by  
-Q<sub>1</sub>;

each Q<sub>1</sub> is independently selected from the group  
5 consisting of -NH<sub>2</sub>, -Cl, -F, -Br, -OH, -R<sub>9</sub>, -NH-R<sub>5</sub>  
wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or -S(O)<sub>2</sub>-R<sub>9</sub>, -OR<sub>5</sub> wherein R<sub>5</sub> is  
-C(O)-R<sub>10</sub>, -OR<sub>9</sub>, -NHR<sub>9</sub>, and



wherein each R<sub>9</sub> and R<sub>10</sub> are independently a -C<sub>1-6</sub>  
straight or branched alkyl group optionally substituted  
15 with -Ar<sub>3</sub> wherein Ar<sub>3</sub> is phenyl;

provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub>  
group which comprises one or more additional -Ar<sub>3</sub>  
groups, said additional -Ar<sub>3</sub> groups are not substituted  
20 with another -Ar<sub>3</sub>.

115. The compound according to claim 114,  
wherein R<sub>3</sub> is -C(O)-Ar<sub>2</sub>,

116. The compound according to claim 114,  
wherein R<sub>3</sub> is -C(O)CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>;

25 117. The compound according to claim 114,  
wherein R<sub>3</sub> is -C(O)-H.

118. The compound according to any one of  
claims 104-117, wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or  
-C(O)C(O)-R<sub>10</sub>.



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119. The compound according to claim 118, wherein  $R_{10}$  is  $Ar_3$ .

120. The compound according to claim 119, wherein:

5  $R_5$  is  $-C(O)-R_{10}$  and  $R_{10}$  is  $Ar_3$ , wherein the  $Ar_3$  cyclic group is phenyl optionally being singly or multiply substituted by:

$-R_9$ , wherein  $R_9$  is a  $C_{1-4}$  straight or branched alkyl group;

10  $-F$ ,

$-Cl$ ,

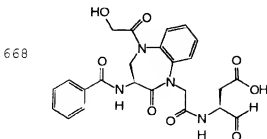
$-N(H)-R_5$ , wherein  $-R_5$  is  $-H$  or  $-C(O)-R_{10}$ , wherein  $R_{10}$  is a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $-Ar_3$ , wherein  $Ar_3$  is

15 phenyl,

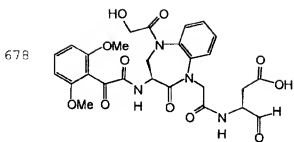
$-N(R_9)(R_{10})$ , wherein  $R_9$  and  $R_{10}$  are independently a  $-C_{1-4}$  straight or branched alkyl group, or

$-O-R_5$ , wherein  $R_5$  is  $H$  or a  $-C_{1-4}$  straight or branched alkyl group.

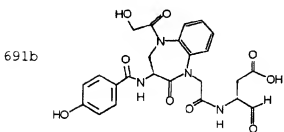
20 121. The compound according to claim 120, selected from the group consisting of:



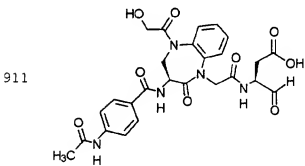
- 916 -



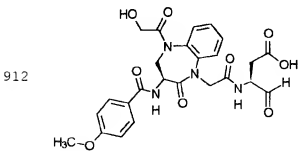
;



;

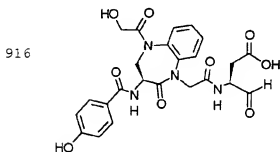
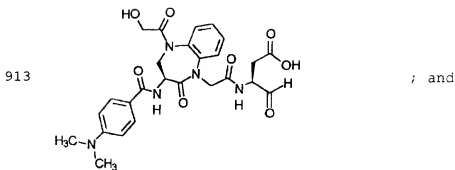


;



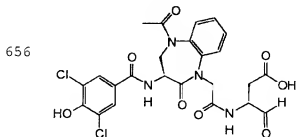
;

- 917 -

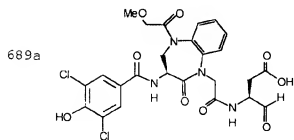
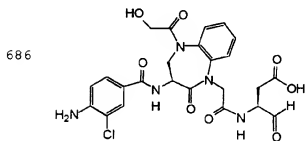
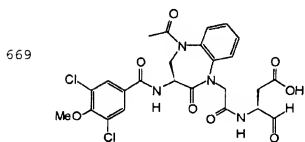
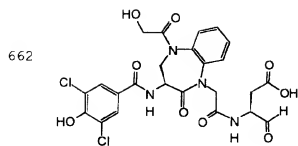


122. The compound according to claim 120,  
 wherein  $Ar_3$  is phenyl being singly or multiply  
 5 substituted at the 3- or 5-position by  $-Cl$  or at the 4-  
 position by  $-NH-R_5$ ,  $-N(R_9)(R_{10})$ , or  $-O-R_5$ .

123. The compound according to claim 122,  
 selected from the group consisting of:

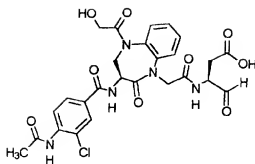


- 918 -

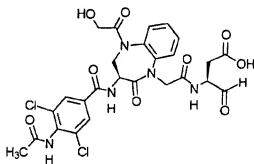


- 919 -

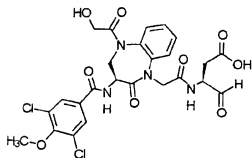
914



915



918

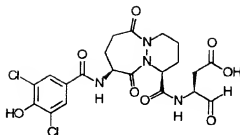


124. The compound according to claim 122,  
 5 selected from the group consisting of:

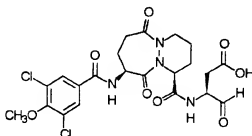
- 920 -

214k

; and



214m



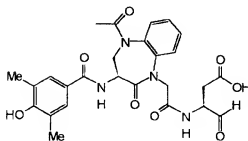
125. The compound according to claim 120,  
 wherein  $Ar_3$  is phenyl being singly or multiply  
 5 substituted at the 3- or 5-position by  $-R_9$ , wherein  $R_9$   
 is a  $C_{1-4}$  straight or branched alkyl group;  
 and at the 4-position by  $-OR_5$ .

126. The compound according to claim 125,  
 selected from the group consisting of:

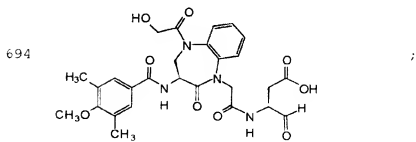
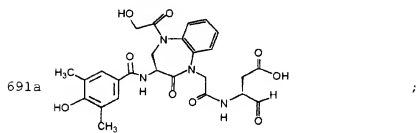
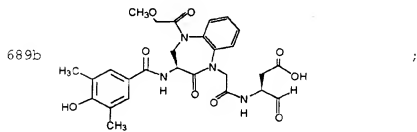
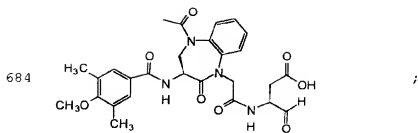
10

671

;

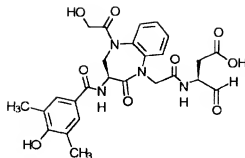


- 921 -



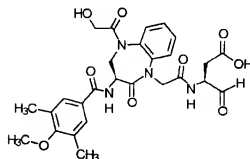
- 922 -

917



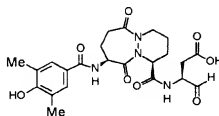
; and

922



127. The compound according to claim 125,  
wherein the compound is:

5 214w



128. The compound according to claim 119,  
wherein:

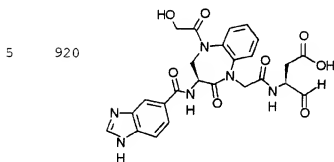
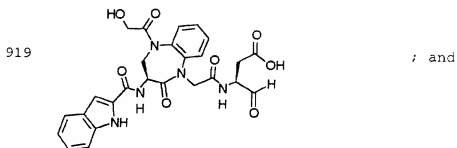
10  $R_5$  is  $-C(O)-R_{10}$ , wherein  $R_{10}$  is  $Ar_3$  and the  $Ar_3$   
cyclic group is selected from the group consisting of  
is indolyl, benzimidazolyl, thienyl, quinolyl,  
isoquinolyl and benzo[b]thiophenyl, and said cyclic  
group optionally being singly or multiply substituted



- 923 -

by  $-Q_1$ .

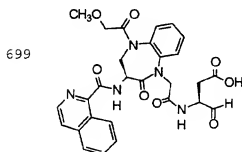
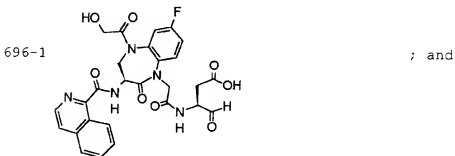
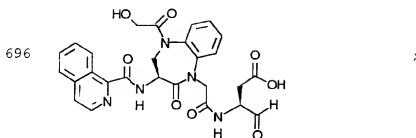
129. The compound according to claim 128,  
selected from the group consisting of:



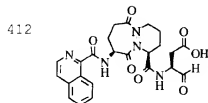
130. The compound according to claim 128,  
wherein the  $Ar_3$  cyclic group is isoquinolyl, and said  
cyclic group optionally being singly or multiply  
substituted by  $-Q_1$ .

10 131. The compound according to claim 130,  
wherein the compound is:

- 924 -



132. The compound according to claim 130,  
 5 wherein the compound is:



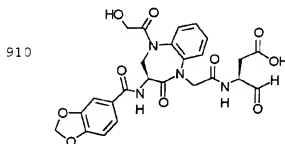
133. The compound according to claim 119,  
 wherein  $R_5$  is  $-C(O)-R_{10}$ , wherein  $R_{10}$  is  $Ar_3$  and the  $Ar_3$

- 925 -

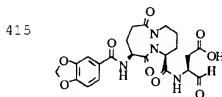
cyclic group is phenyl, substituted by



134. The compound according to claim 133,  
wherein the compound is:



10 135. The compound according to claim 133,  
wherein the compound is:



136. A pharmaceutical composition, comprising  
a compound according to any one of claims 1-41 and 57-  
15 135 in an amount effective for decreasing IGIF  
production and a pharmaceutically acceptable carrier.

137. A pharmaceutical composition comprising  
a compound according to any one of claims 1-41 and 57-  
135 in an amount effective for decreasing IFN- $\gamma$

- 926 -

production and a pharmaceutically acceptable carrier.

138. A method for treating or preventing a disease selected from an IGIF mediated disease, an IFN- $\gamma$  mediated disease, an inflammatory disease, an autoimmune disease, an infectious disease, a proliferative disease, a neurodegenerative disease, a necrotic disease, osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, cerebral ischemia, myocardial ischemia, adult respiratory distress syndrome, infectious hepatitis, sepsis, septic shock, Shigellosis, glomerulonephritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), juvenile diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, myasthenia gravis, multiple sclerosis, psoriasis, lichenplanus, graft vs. host disease, acute dermatomyositis, eczema, primary cirrhosis, hepatitis, uveitis, Behcet's disease, acute dermatomyositis, atopic skin disease, pure red cell aplasia, aplastic anemia, amyotrophic lateral sclerosis and nephrotic syndrome comprising the step of administering to said patient a pharmaceutical composition according to claims 136 or 137.

139. The method according to claim 138, wherein the disease is selected from an inflammatory disease, an autoimmune disease, an infectious disease, rheumatoid arthritis, ulcerative colitis, Crohn's disease, hepatitis, adult respiratory distress syndrome, glomerulonephritis, insulin-dependent

- 927 -

diabetes mellitus (Type I), juvenile diabetes, psoriasis, graft vs. host disease, and hepatitis.

140. A process for preparing an N-acylamino compound, comprising the steps of:

5           a)    mixing a carboxylic acid with an N-alloc-protected amine in the presence of an inert solvent, triphenylphosphine, a nucleophilic scavenger, and tetrakis-triphenyl phosphine palladium(0) at ambient temperature under an inert atmosphere; and

10           b)    adding to the step a) mixture, HOBT and EDC; and optionally comprising the further step of:

            c)    hydrolyzing the step b) mixture in the presence of a solution comprising an acid and H<sub>2</sub>O, wherein the step b) mixture is optionally concentrated.

15

141. The process according to claim 140, wherein the inert solvent is CH<sub>2</sub>Cl<sub>2</sub>, DMF, or a mixture of CH<sub>2</sub>Cl<sub>2</sub> and DMF.

142. The process according to claim 140, wherein the nucleophilic scavenger is dimedone, morpholine, trimethylsilyl dimethylamine or dimethyl barbituric acid.

20

143. The process according to claim 142, wherein the nucleophilic scavenger is trimethylsilyl dimethylamine or dimethyl barbituric acid.

25

144. The process according to claim 142, wherein the inert solvent is CH<sub>2</sub>Cl<sub>2</sub>, DMF, or a mixture

- 928 -

of  $\text{CH}_2\text{Cl}_2$  and DMF.

145. The process according to claim 144, wherein the nucleophilic scavenger is dimethyl barbituric acid.

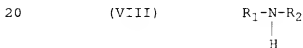
5                   146. The process according to claim 145, wherein the solution comprises trifluoroacetic acid in about 1-90% by weight.

10                   147. The process according to claim 146, wherein the solution comprises trifluoroacetic acid in about 20-50% by weight.

148. The process according to claim 145, wherein the solution comprises hydrochloric acid in about 0.1-30% by weight.

15                   149. The process according to claim 148, wherein the solution comprises hydrochloric acid in about 5-15% by weight.

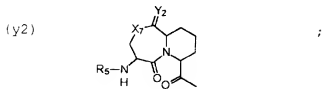
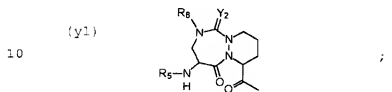
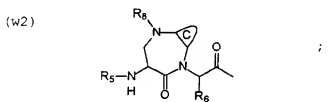
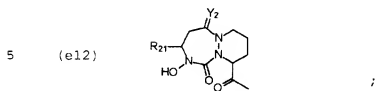
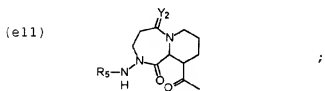
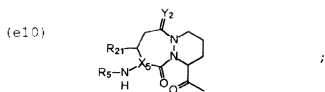
150. The process according to any one of claims 140-149, wherein the N-acylamino compound is represented by formula (VIII):



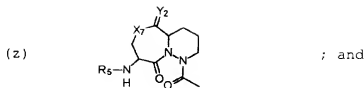
wherein:

25                    $\text{R}_1$  is selected from the group consisting of the following formulae:

- 929 -

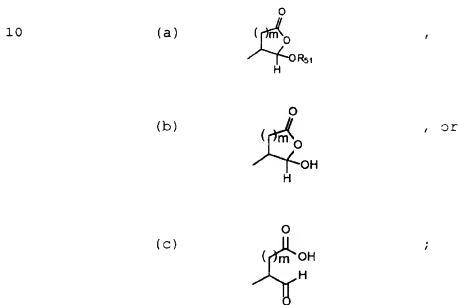


- 930 -



C is a ring chosen from the set consisting of benzo, pyrido, thiero, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl, the ring optionally being  
 5 singly or multiply substituted by halogen,  $-NH_2$ , or  $-NH-R_9$ ;

$R_2$  is:



15 m is 1 or 2;

each  $R_5$  is independently selected from the group consisting of:





- 931 -

-C(O)O-R<sub>9</sub>,  
 -C(O)-N(R<sub>10</sub>)(R<sub>10</sub>)  
 -S(O)<sub>2</sub>-R<sub>9</sub>,  
 -S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
 5 -C(O)-CH<sub>2</sub>-O-R<sub>9</sub>,  
 -C(O)C(O)-R<sub>10</sub>,  
 -R<sub>9</sub>,  
 -H,  
 -C(O)C(O)-OR<sub>10</sub>, and  
 10 -C(O)C(O)-N(R<sub>9</sub>)(R<sub>10</sub>);

X<sub>5</sub> is CH or N;

Y<sub>2</sub> is H<sub>2</sub> or O;

15 X<sub>7</sub> is -N(R<sub>8</sub>)- or -O-;

R<sub>6</sub> is selected from the group consisting of -H and -CH<sub>3</sub>;

R<sub>8</sub> is selected from the group consisting of:

20 -C(O)-R<sub>10</sub>,  
 -C(O)O-R<sub>9</sub>,  
 -C(O)-N(H)-R<sub>10</sub>,  
 -S(O)<sub>2</sub>-R<sub>9</sub>,  
 -S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
 -C(O)-CH<sub>2</sub>-OR<sub>10</sub>,  
 25 -C(O)C(O)-R<sub>10</sub>,  
 -C(O)-CH<sub>2</sub>N(R<sub>10</sub>)(R<sub>10</sub>),  
 -C(O)-CH<sub>2</sub>C(O)-O-R<sub>9</sub>,  
 -C(O)-CH<sub>2</sub>C(O)-R<sub>9</sub>,  
 -H, and  
 30 -C(O)-C(O)-OR<sub>10</sub>;

- 932 -

each  $R_9$  is independently selected from the group consisting of  $-Ar_3$  and a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $-Ar_3$ , wherein the  $-C_{1-6}$  alkyl group is optionally unsaturated;

- 5        each  $R_{10}$  is independently selected from the group consisting of  $-H$ ,  $-Ar_3$ , a  $-C_{3-6}$  cycloalkyl group, and a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $-Ar_3$ , wherein the  $-C_{1-6}$  alkyl group is optionally unsaturated;

- 10        $R_{13}$  is selected from the group consisting of  $H$ ,  $Ar_3$ , and a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $-Ar_3$ ,  $-CONH_2$ ,  $-OR_5$ ,  $-OH$ ,  $-OR_9$ , or  $-CO_2H$ ;

- 15       each  $R_{51}$  is independently selected from the group consisting of  $R_9$ ,  $-C(O)-R_9$ ,  $-C(O)-N(H)-R_9$ , or each  $R_{51}$  taken together forms a saturated 4-8 member carbocyclic ring or heterocyclic ring containing  $-O-$ ,  $-S-$ , or  $-NH-$ ;

- 20       each  $R_{21}$  is independently selected from the group consisting of  $-H$  or a  $-C_{1-6}$  straight or branched alkyl group;

- 25       each  $Ar_3$  is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from  $-O-$ ,  $-S-$ ,  $-SO-$ ,  $SO_2$ ,  $=N-$ , and  $-NH-$ , said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally

- 933 -

comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

- 5 each  $Q_1$  is independently selected from the group consisting of  $-\text{NH}_2$ ,  $-\text{CO}_2\text{H}$ ,  $-\text{Cl}$ ,  $-\text{F}$ ,  $-\text{Br}$ ,  $-\text{I}$ ,  $-\text{NO}_2$ ,  $-\text{CN}$ ,  $=\text{O}$ ,  $-\text{OH}$ ,  $-\text{perfluoro C}_{1-3}$  alkyl,  $\text{R}_5$ ,  $-\text{OR}_5$ ,  $-\text{NHR}_5$ ,  $-\text{OR}_9$ ,  $-\text{N}(\text{R}_9)(\text{R}_{10})$ ,  $-\text{R}_9$ ,  $-\text{C}(\text{O})-\text{R}_{10}$ , and

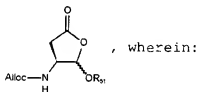
10



- 15 provided that when  $-\text{Ar}_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-\text{Ar}_3$  groups, said additional  $-\text{Ar}_3$  groups are not substituted with another  $-\text{Ar}_3$ ;

151. The process according to any one of claims 140 -149 wherein the N-alloc protected amine is:

20



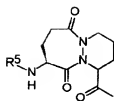
$\text{R}_{51}$  is independently selected from the group consisting of  $\text{R}_9$ ,  $-\text{C}(\text{O})-\text{R}_9$ ,  $-\text{C}(\text{O})-\text{N}(\text{H})-\text{R}_9$ , or each  $\text{R}_{51}$  taken together forms a saturated 4-6 member carbocyclic ring or heterocyclic ring containing  $-\text{O}-$ ,  $-\text{S}-$ , or  $-\text{NH}-$ ;

25

152. The process according to any one of claims 140-149, wherein  $\text{R}_1$  is:

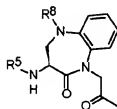
- 934 -

(A-e10)



153. The process according to any one of claims 140-149, wherein R<sub>1</sub> is:

5 (A-w2)



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FIG. 1A

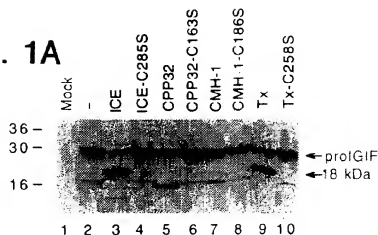


FIG. 1B

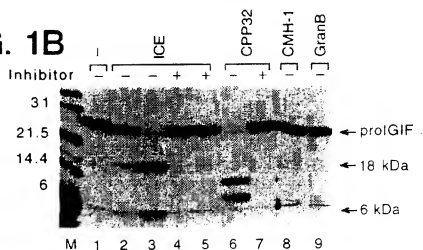


FIG. 1C

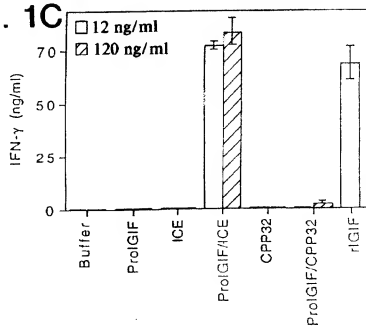


FIG. 2A

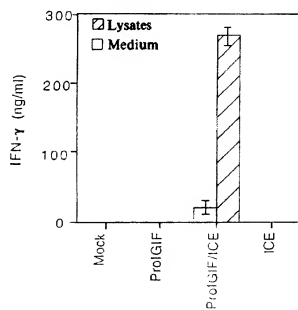
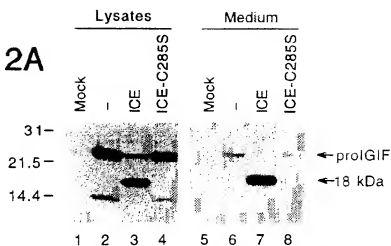


FIG. 2B

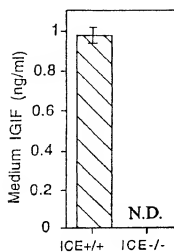


FIG. 3A

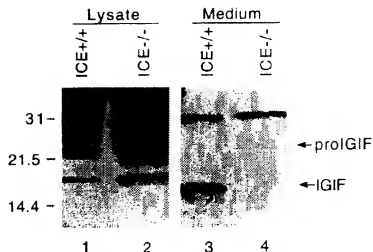


FIG. 3B

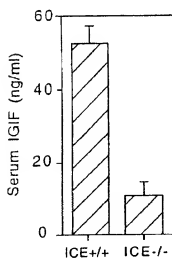


FIG. 3C

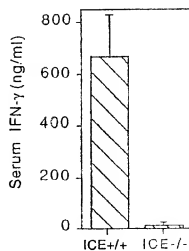


FIG. 3D

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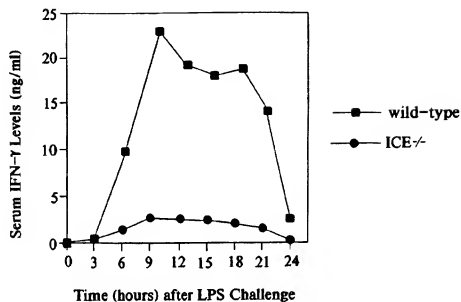


FIG. 4

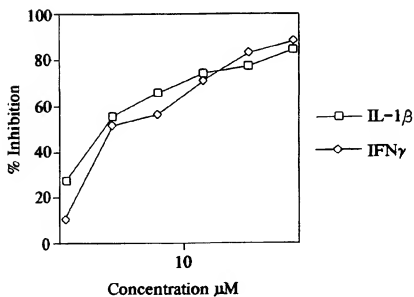


FIG. 5



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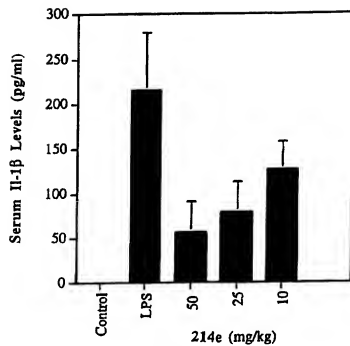


FIG. 6

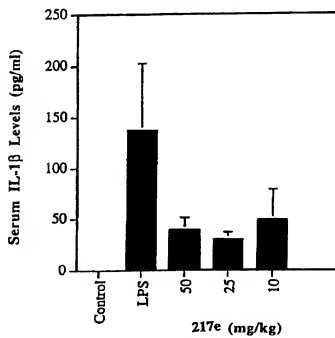


FIG. 7

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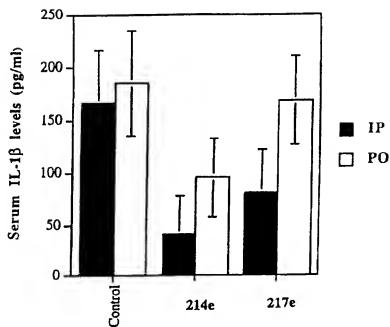


FIG. 8

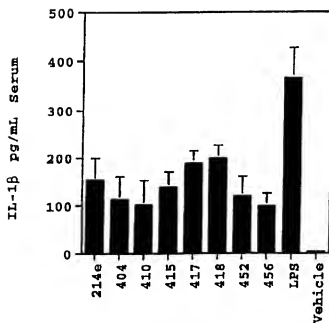


FIG. 9

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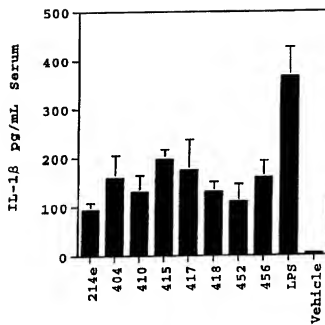
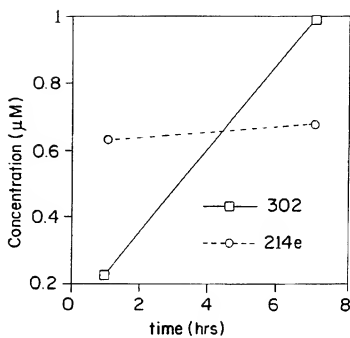
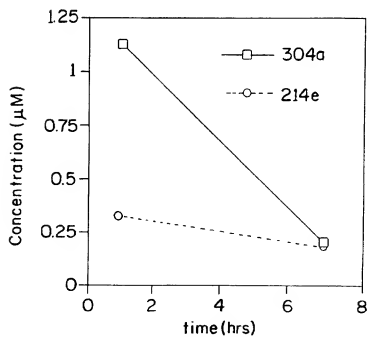


FIG. 10

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**FIG. 11A****FIG. 11B**

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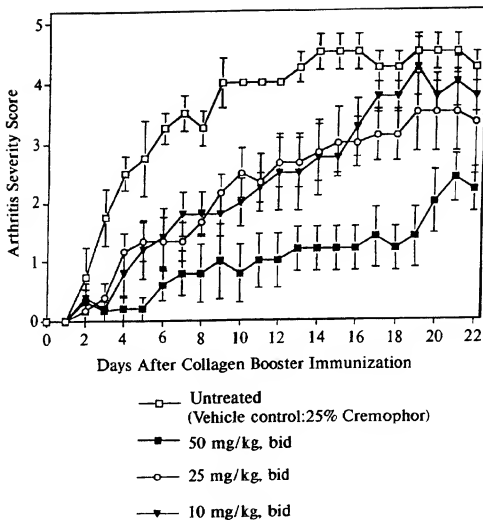


FIG. 12

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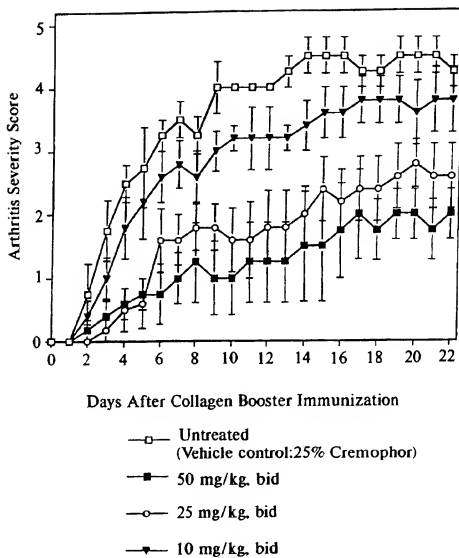


FIG. 13

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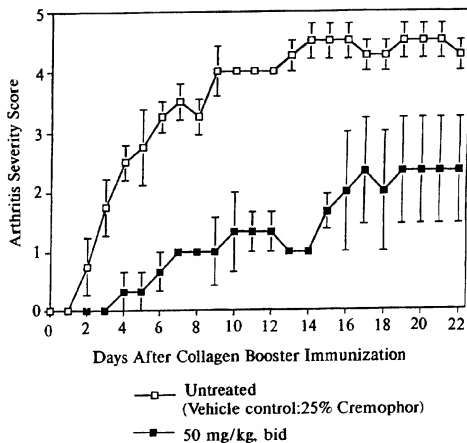


FIG. 14



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

|  |                              |           |   |
|--|------------------------------|-----------|---|
| (51) International Patent Classification <sup>6</sup> :<br><b>C07K 5/023, C07D 487/04, 498/04, A61K 38/04, 31/55 // (C07D 487/04, 243:00, 237/00)</b>  |                              | <b>A3</b> | (11) International Publication Number:<br><b>WO 97/22619</b>    |
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| 08/712,878   | 12 September 1996 (12.09.96) | US        |   |
| 60/031,495   | 26 November 1996 (26.11.96)  | US        |   |
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| (74) Agents: HALEY, James, F., Jr. et al.; Fish & Neave, 1251 Avenue of the Americas, New York, NY 10020-1104 (US).  |                              |           |   |
| (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, ST, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TR, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).   |                              |           |   |
| <p><b>Published</b><br/> <i>With international search report.<br/>         Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>  |                              |           |   |
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(54) Title: INHIBITORS OF INTERLEUKIN- $\beta$  CONVERTING ENZYME

(57) Abstract

The present invention relates to novel classes of compounds which are inhibitors of interleukin- $\beta$  converting enzyme. The ICE inhibitors of this invention are characterized by specific structural and physicochemical features. This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting ICE activity and consequently, may be advantageously used as agents against IL-1-, apoptosis-, IGIF-, and IFN- $\gamma$ -mediated diseases, inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases, degenerative diseases, and necrotic diseases. This invention also relates to methods for inhibiting ICE activity, for treating interleukin-1-, apoptosis-, IGIF- and IFN- $\gamma$ -mediated diseases and decreasing IGIF and IFN- $\gamma$  production using the compounds and compositions of this invention. This invention also relates to methods for preparing N-acylamino compounds.



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# INTERNATIONAL SEARCH REPORT

Intern. al Application No  
PCT/US 96/20843

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07K5/023 C07D487/04 C07D498/04 A61K38/04 A61K31/55  
// (C07D487/04, 243:00, 237:00)

According to International Patent Classification (IPC) or to both national classification and IPC

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

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|------------|--|-----------------------|
| X          | EP 0 135 349 A (TAKEDA CHEMICAL INDUSTRIES LTD) 27 March 1985<br>see claims 1-4,41-43; examples 24,25<br>---<br>-/-- | 1,42-56,<br>136-139   |

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Date of the actual completion of the international search

28 August 1997

Date of mailing of the international search report

04.09.97

Name and mailing address of the ISA

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## INTERNATIONAL SEARCH REPORT

Intern. al Application No.

PCT/US 96/20843

## C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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| X          | WO 95 33751 A (SANOFI WINTHROP INC) 14 December 1995  | 4-8,<br>16-38,<br>40-57,<br>59-62,<br>64-81,<br>86-90,<br>92, 94,<br>95,<br>97-99,<br>101-103,<br>114-120,<br>122 |
| X          | see the whole document  | 124, 125,<br>127, 128,<br>130, 132,<br>133,<br>135-139  |
| P, X       | WO 95 35308 A (VERTEX PHARMA) 28 December 1995<br>see the whole document  | 1-8,<br>14-139  |
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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 96/20843

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 55,56,138,139  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claim(s) 55,56,138,139  
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body, the search has been carried out and based on the alleged  
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2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

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1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
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covers only those claims for which fees were paid, specifically claims Nos.:  
  
Subject 1: Claims 1-13,14,15,39,58,63,82-85,91,93,96,100,104-113,121,123,126,  
129,131,134(complete); 4-8,42-57,62,80,81,88-90,92,95,98,99,102,118-120,122,125,  
128,130,133,136-139(partially).  
See next page
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

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International Application No. PCT/US 96/ 20843

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

Subject 2: Claims 16-38,40,41,59-61,64-79,86,87,94,97,101,103,114-117,124,127,132,135(complete); 4-8,42-57,62,80,81,88-90,92,95,98,99,102,118-120,122,125,128,130,133,136-139(partially

# INTERNATIONAL SEARCH REPORT

Information on patent family members

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Information on patent family members

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